Systemic Hyperalgesia in Females with Gulf War Illness, Chronic Fatigue Syndrome and Fibromyalgia.

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Abstract

Pain is a diagnostic criterion for Gulf War Illness (GWI), Chronic Fatigue Syndrome (CFS), and fibromyalgia (FM). The physical sign of systemic hyperalgesia (tenderness) was assessed in 920 women who were stratified by 2000 Kansas GWI, 1994 CFS, and 1990 FM criteria. Pressure was applied by dolorimetry at 18 traditional tender points and the average pressure causing pain determined. GWI women were the most tender (2.9 ± 1.6 kg, mean $\pm$ SD, n = 70), followed by CFS/FM (3.1 ± 1.4 kg, n = 196), FM (3.9 ± 1.4 kg, n = 56), and CFS (5.8 ± 2.1 kg, n = 170) compared to controls (7.2 ± 2.4 kg, significantly highest by Mann-Whitney tests p < 0.0001, n = 428). Receiver operating characteristics set pressure thresholds of 4.0 kg to define GWI and CFS/FM (specificity 0.85, sensitivities 0.80 and 0.83, respectively), 4.5 kg for FM, and 6.0 kg for CFS. Pain, fatigue, quality of life, and CFS symptoms were equivalent for GWI, CFS/FM and CFS. Dolorimetry correlated with symptoms in GWI but not CFS or FM. Therefore, women with GWI, CFS and FM have systemic hyperalgesia compared to sedentary controls. The physical sign of tenderness may complement the symptoms of the Kansas criteria as a diagnostic criterion for GWI females, and aid in the diagnosis of CFS. Molecular mechanisms of systemic hyperalgesia may provide new insights into the neuropathology and treatments of these nociceptive, interoceptive and fatiguing illnesses.

Acetylcholinesterase inhibitor exposures as an initiating factor in the development of Gulf War Illness, a chronic neuroimmune disorder in deployed veterans.

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Abstract

Gulf War Illness (GWI) is a chronic multi-symptom disorder, characterized by symptoms such as fatigue, pain, cognitive and memory impairment, respiratory, skin and gastrointestinal problems, that is experienced by approximately one-third of 1991 Gulf War veterans. Over the nearly three decades since the end of the war, investigators have worked to elucidate the initiating factors and underlying causes of GWI. A significant portion of this research has indicated a strong correlation between GWI and exposure to a number of different acetycholinesterase inhibitors (AChEIs) in theater, such as sarin and cyclosarin nerve agents, chlorpyrifos and dichlorvos pesticides, and the anti-nerve agent prophylactic pyridostigmine bromide. Through studying these exposures and their relationship to the symptoms presented by ill veterans, it has become increasingly apparent that GWI is the likely result of an underlying neuroimmune disorder. While evidence indicates that AChEIs are a key exposure in the development of GWI, particularly organophosphate AChEIs, the mechanism(s) by which these chemicals instigate illness appears to be related to "off-target", non-cholinergic effects. In this review, we will discuss the role of AChEI exposure in the development and persistence of GWI; in particular, how these chemicals, combined with other exposures, have led to a chronic neuroimmune disorder.

The Gulf War Women's Health Cohort: Study Design and Protocol.

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Abstract

Military service and deployment affect women differently than men, underscoring the need for studies of the health of women veterans and their receipt of health care services. Despite the large numbers of women who served during the 1990-1991 Gulf War, few studies have evaluated Gulf War illness (GWI) and other medical conditions specifically as they affect women veterans of the 1991 Gulf War. The objectives of the Gulf War Women's Health Cohort study are: (1) to establish the Gulf War women's cohort (GWWC), a large sample of women veterans who served in the 1990-1991 Gulf War and a comparison group of women who served in other locations during that period; and (2) to provide current, comprehensive data on the health status of women who served during the 1990-1991 Gulf War, and identify any specific conditions that affect Gulf War women veterans at excess rates. The study will utilize both existing datasets and newly collected data to examine the prevalence and patterns of Gulf War Illness symptoms, diagnosed medical conditions, reproductive health, birth outcomes and other health issues among women who served during the Gulf War. The Gulf War Women's Health Cohort study will address the need for information about the comprehensive health of women veterans who were deployed to the Gulf War, and other wars during the Gulf War era.

Prevalence and Patterns of Symptoms Among Female Veterans of the 1991 Gulf War Era: 25 Years Later.

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Abstract

Background: A new national cohort of Gulf War (GW) veterans of 1,318 participants was created from the Veterans Affairs Cooperative Studies Program 585 Gulf War Era Cohort and Biorepository (GWECB) pilot study. However, female veteran health outcomes have not been reported separately for those deployed versus nondeployed to the 1990-1991 GW.

Methods: Using data from the cooperative studies program (CSP) #585 GWECB, this study examined whether excess prevalence and patterns of Gulf War Illness (GWI) symptoms were present among female veterans who served during the GW compared with female veterans who did not deploy to the GW (GW-Era).

Results: A total of 301 women veterans participated in the survey (203 GW, 98 GW-era). Mean ages in 2016 were 53 years among GW women veterans and 54 years among GW-era women. Participant groups did not differ by age, race, ethnicity, or education, but GW women were more likely to have served in the army or navy and less likely to have served in the air force. Compared with GW-era women, GW-deployed women were significantly more likely to report 7 out of 34 symptoms related to cognitive, neurological, and mood problems and respiratory complaints when controlling for age, race, GW deployment, branch of service, and smoking status in logistic regression analyses. Ordered logistic regression was also used to estimate the association between the total number of self-reported symptoms and deployment status, age, race, branch of service, and smoking status. Results showed deployed GW veterans to have a nearly twofold risk of reporting more symptoms than GW-era women, with younger, nonwhite, army-enlisted GW women significantly more likely to report more total symptoms.

Discussion: Twenty-five years after the war, GWECB women GW veterans continued to report a wide variety of symptoms at a significantly higher excess frequency prevalence than GW-era women. Our results showed at least a 14% excess frequency prevalence in all seven significantly different symptoms encompassing two out of the six Kansas GWI criteria, including neurological/mood/cognition, and respiratory domains. These results suggest that further study of these symptom domains is warranted in GW women veterans.

Targeting sirtuin activity with nicotinamide riboside reduces neuroinflammation in a GWI mouse model.

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Abstract

Gulf War Illness (GWI) affects 30% of veterans from the 1991 Gulf War (GW), who suffer from symptoms that reflect ongoing mitochondria dysfunction. Brain mitochondria bioenergetics dysfunction in GWI animal models corresponds with astroglia activation and neuroinflammation. In a pilot study of GW veterans (n = 43), we observed that blood nicotinamide adenine dinucleotide (NAD) and sirtuin 1 (Sirt1) protein levels were decreased in the blood of veterans with GWI compared to healthy GW veterans. Since nicotinamide riboside (NR)-mediated targeting of Sirt1 is shown to improve mitochondria function, we tested whether NR can restore brain bioenergetics and reduce neuroinflammation in a GWI mouse model. We administered a mouse diet supplemented with NR at 100μg/kg daily for 2-months to GWI and control mice (n = 27). During treatment, mice were assessed for fatigue-type behavior using the Forced Swim Test (FST), followed by euthanasia for biochemistry and immunohistochemistry analyses. Fatigue-type behavior was elevated in GWI mice compared to control mice and lower in GWI mice treated with NR compared to untreated GWI mice. Levels of plasma NAD and brain Sirt1 were low in untreated GWI mice, while GWI mice treated with NR had higher levels, similar to those of control mice. Deacetylation of the nuclear-factor κB (NFκB) p65 subunit and peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α) was an increase in the brains of NR-treated GWI mice. This corresponded with a decrease in pro-inflammatory cytokines and lipid peroxidation and an increase in markers of mitochondrial bioenergetics in the brains of GWI mice. These findings suggest that targeting NR mediated Sirt1 activation restores brain bioenergetics and reduces inflammation in GWI mice. Further evaluation of NR in GWI is warranted to determine its potential efficacy in treating GWI.

Leveraging Prior Knowledge to Recover Characteristic Immune Regulatory Motifs in Gulf War Illness.

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Abstract

Potentially linked to the basic physiology of stress response, Gulf War Illness (GWI) is a debilitating condition presenting with complex immune, endocrine and neurological symptoms. Here we interrogate the immune response to physiological stress by measuring 16 blood-borne immune markers at 8 time points before, during and after maximum exercise challenge in $n = 12$ GWI veterans and $n = 11$ healthy veteran controls deployed to the same theater. Immune markers were combined into functional sets and the dynamics of their joint expression described as classical rate equations. These empirical networks were further informed structurally by projection onto prior knowledge networks mined from the literature. Of the 49 literature-informed immune signaling interactions, 21 were found active in the combined exercise response data. However, only 4 signals were common to both subject groups while 7 were uniquely active in GWI and 10 uniquely active in healthy veterans. Feedforward mediation of IL-23 and IL-17 by IL-6 and IL-10 emerged as distinguishing control elements that were characteristically active in GWI versus healthy subjects. Simulated restructuring of the regulatory circuitry in GWI as a result of applying an IL-6 receptor antagonist in combination with either a Th1 (IL-2, IFNγ, and TNFα) or IL-23 receptor antagonist predicted a partial rescue of immune response elements previously associated with illness severity. Overall, results suggest that pharmacologically altering the topology of the immune response circuitry identified as active in GWI can inform on strategies that while not curative, may nonetheless deliver a reduction in symptom burden. A lasting and more complete remission in GWI may therefore require manipulation of a broader physiology, namely one that includes endocrine oversight of immune function.

Brain and Physiological Markers of Autonomic Function Are Associated With Treatment-Related Improvements in Self-Reported Autonomic Dysfunction in Veterans With Gulf War Illness: An Exploratory Pilot Study.

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Abstract

Background: Gulf War Illness (GWI) is a poorly understood condition characterized by a constellation of mood, cognitive, and physical symptoms. A growing body of evidence demonstrates autonomic nervous system (ANS) dysfunction. Few published treatment studies exist for GWI.

Method: We recently completed a randomized controlled trial comparing a 10-week group yoga intervention to 10-week group cognitive behavioral therapy (CBT) for veterans with GWI. Here, we present exploratory data on ANS biomarkers of treatment response from a small pilot exploratory neurophysiological add-on study (n = 13) within that larger study.

Results: Findings suggest that veterans with GWI receiving either yoga or CBT for pain improved following treatment and that changes in biological ANS-especially for the yoga group-moved in the direction of healthy profiles: lower heart rate, higher square root of the mean squared differences between successive R-R intervals (RMSSD), greater parasympathetic activation/dominance (increased high-frequency heart rate variability [HF-HRV], decreased low-frequency/high-frequency [LF/HF] ratio), reduced right amygdala volume, and stronger amygdala-default mode/amygdala-salience network connectivity, both immediately posttreatment and at 6-month follow-up. Biological mechanisms of CBT appeared to underlie improvements in more psychologically loaded symptoms such as self-reported fatigue and energy. Higher tonic arousal and/or more sympathetic dominance (higher skin conductance, lower RMSSD, lower HF-HRV, higher LF/HF ratio) pretreatment predicted greater treatment-related improvements in self-reported ANS for both the yoga and CBT group.

Conclusion: These exploratory pilot data provide preliminary support for the suggestion that treatment (yoga, CBT) is associated with improvements in both biological and self-reported ANS dysfunctions in GWI. The major limitation for these findings is the small sample size. Larger and more controlled studies are needed to replicate these findings and directly compare biomarkers of yoga versus CBT.

Vaccine-Induced Adverse Effects in Cultured Neuroblastoma 2A (N2A) Cells Duplicate Toxicity of Serum from Patients with Gulf War Illness (GWI) and Are Prevented in the Presence of Specific Anti-Vaccine Antibodies.

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Abstract

Gulf War illness (GWI) is a chronic disease of unknown etiology affecting over 200,000 veterans with symptoms including neurocognitive problems. We previously demonstrated GWI serum toxicity on neural cell cultures manifested by compromised neural network function, decreased cell spreading, and enhanced cell apoptosis. These patients lacked six human leukocyte antigen (HLA) class II alleles, resulting in an inability to form antibodies. Therefore, we hypothesized that GWI patients have vaccine-derived, persistent pathogens, which contribute to the development of the disease. Here, we examined whether individual vaccines were toxic in cultured N2A cells. Moreover, we used antibodies against each of the 20 vaccines administered to Gulf War (GW) veterans, to examine the effects of these antibodies on cell spreading and apoptosis in N2A cells. Antibodies against cholera toxin, hepatitis B, hemagglutinin H1N1, H3N2, and B from influenza A and B strains, measles, and *Salmonella Typhi* polysaccharide Vi had a remarkable protective effect on both cell spreading and apoptosis, whereas none of the other antibodies administered to GW veterans had an effect. The in vitro observed adverse effects of GWI serum may be due in part to vaccine-derived pathogens, antibodies against which had a protective effect in N2A cell cultures.

Safety, Tolerability and Efficacy of Dietary Supplementation with Concord Grape Juice in Gulf War Veterans with Gulf War Illness: A Phase I/IIA, Randomized, Double-Blind, Placebo-Controlled Trial.

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Abstract

Approximately 30 percent of U.S. veterans deployed during the Gulf War (1990-1991) have been diagnosed with Gulf War Illness (GWI), a chronic multi-symptom disorder without widely available specific treatments. We investigated whether the consumption of Concord grape juice (CGJ), rich in anti-inflammatory flavonoids, would be tolerated and safe in individuals with GWI and explored improvement in cognitive function and fatigue. Thirty-six veterans with GWI enrolled in a 24-week randomized, double-blind, Phase I/IIA clinical trial to explore safety, tolerability, and feasibility of 16 ounces daily of commercially available CGJ compared to placebo. Participants completed neurocognitive tests and self-reported surveys at baseline, 12 and 24 weeks. Thirty-one participants (86%) completed the study; no dropouts were related to side effects. Thirty participants (83%) documented ≥80% adherence. There were no statistically significant unadjusted differences between CGJ and placebo groups in change in efficacy measures from baseline to endpoint. We employed general linear regression models controlling for baseline differences between groups which indicated statistically significant improvement in the Halstead Category Test-Russell Revised Version (RCAT) at endpoint in the CGJ group compared to placebo (8.4 points, $p = 0.04$). Other measures of cognitive functioning did not indicate significant improvements in the adjusted analyses (p-values: 0.09-0.32), nor did the fatigue variable ($p = 0.67$). CGJ was safe and well-tolerated by veterans with GWI. Our data suggest high tolerability and potential benefit from CGJ in veterans with GWI and can be used to inform future studies of efficacy.

Logistic Regression Algorithm Differentiates Gulf War Illness (GWI) Functional Magnetic Resonance Imaging (fMRI) Data from a Sedentary Control.

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Abstract

Gulf War Illness (GWI) is a debilitating condition characterized by dysfunction of cognition, pain, fatigue, sleep, and diverse somatic symptoms with no known underlying pathology. As such, uncovering objective biomarkers such as differential regions of activity within a Functional Magnetic Resonance Imaging (fMRI) scan is important to enhance validity of the criteria for diagnosis. Symptoms are exacerbated by mild activity, and exertional exhaustion is a key complaint amongst sufferers. We modeled this exertional exhaustion by having GWI (n = 80) and sedentary control (n = 31) subjects perform submaximal exercise stress tests on two consecutive days. Cognitive differences were assessed by comparing fMRI scans performed during 2-Back working memory tasks before and after the exercise. Machine learning algorithms were used to identify differences in brain activation patterns between the two groups on Day 1 (before exercise) and Day 2 (after exercise). The numbers of voxels with t > 3.17 (corresponding to p < 0.001 uncorrected) were determined for brain regions defined by the Automated Anatomical Labeling (AAL) atlas. Data were divided 70:30 into training and test sets. Recursive feature selection identified twenty-nine regions of interest (ROIs) that significantly distinguished GWI from control on Day 1 and 28 ROIs on Day 2. Ten regions were present in both models between the two days, including right anterior insula, orbital frontal cortex, thalamus, bilateral temporal poles, and left supramarginal gyrus and cerebellar Crus 1. The models had 70% accuracy before exercise on Day 1 and 85% accuracy after exercise on Day 2, indicating the logistic regression model significantly differentiated subjects with GWI from the sedentary control group. Exercise caused changes in these patterns that may indicate the cognitive differences caused by exertional exhaustion. A second set of predictive models was able to classify previously identified GWI exercise subgroups START, STOPP, and POTS for both Days 1 and Days 2 with 67% and 69% accuracy respectively. This study was the first of its kind to differentiate GWI and the three sub-phenotypes START, STOPP, and POTS from a sedentary control using a logistic regression estimation method.

Effects of a high fat diet on gut microbiome dysbiosis in a mouse model of Gulf War Illness.

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Abstract

Gulf War Illness (GWI) is a chronic health condition that appeared in Veterans after returning home from the Gulf War. The primary symptoms linked to deployment are posttraumatic stress disorder, mood disorders, GI problems and chronic fatigue. At first glance, these symptoms are difficult to ascribe to a single pathological mechanism. However, it is now clear that each symptom can be linked individually to alterations in the gut microbiome. The primary objective of the present study was to determine if gut microbiome dysbiosis was evident in a mouse model of GWl. Because the majority of Gulf War Veterans are overweight, a second objective was to determine if a high fat diet (HF) would alter GWI outcomes. We found that the taxonomic structure of the gut microbiome was significantly altered in the GWI model and after HF exposure. Their combined effects were significantly different from either treatment alone. Most treatment-induced changes occurred at the level of phylum in Firmicutes and Bacteroidetes. If mice fed HF were returned to a normal diet, the gut microbiome recovered toward normal levels in both controls and GWI agent-treated mice. These results add support to the hypotheses that dysbiosis in the gut microbiome plays a role in GWI and that life-style risk factors such as an unhealthy diet can accentuate the effects of GWI by impacting the gut microbiome. The reversibility of the effect of HF on the gut microbiome suggests new avenues for treating GWI through dietary intervention.

Genome-wide Transcriptome Architecture in a Mouse Model of Gulf War Illness.

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Abstract

Gulf War Illness (GWI) is thought to be a chronic neuroimmune disorder caused by in-theater exposure during the 1990-1991 Gulf War. There is a consensus that the illness is caused by exposure to insecticides and nerve agent toxicants. However, the heterogeneity in both development of disease and clinical outcomes strongly suggests a genetic contribution. Here, we modeled GWI in 30 BXD recombinant inbred strains with a combined treatment of corticosterone (CORT) and diisopropyl fluorophosphate (DFP). We quantified transcriptomes from 409 prefrontal cortex samples. Compared to the untreated and DFP treated controls. The combined treatment significantly activated pathways such as cytokine-cytokine receptor interaction and TNF signaling pathway. Protein-protein interaction analysis defined 6 subnetworks for CORT+DFP, with the key regulators being Cxcl1, Il6, Ccnb1, Tnf, Agt, and Itgam. We also identified 21 differentially expressed genes having significant QTLs related to CORT+DFP, but without evidence for untreated and DFP treated controls, suggesting regions of the genome specifically involved in the response to CORT+DFP. We identified Adamts9 as a potential contributor to response to CORT+DFP and found links to symptoms of GWI. Furthermore, we observed a significant effect of CORT+DFP treatment on the relative proportion of myelinating oligodendrocytes, with a QTL on Chr5. We highlight three candidates, Magi2, Sema3c, and Gnai1, based on their high expression in the brain and oligodendrocyte. In summary, our results show significant genetic effects of the CORT+DFP treatment, which mirrors gene and protein expression changes seen in GWI sufferers, providing insight into the disease and a testbed for future interventions.

Neurotoxicity in Gulf War Illness and the Potential Role of Glutamate.

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Abstract

Shortly after the Gulf War in 1990-1991, service men and women began reporting multiple symptoms ranging from persistent headaches, widespread pain, chronic fatigue, cognitive dysfunction, mood dysregulation, gastrointestinal issues, skin abnormalities, and respiratory problems. This prompted the Centers for Disease Control and Prevention (CDC) to initially classify the disorder as chronic multi-symptom illness (CMI), where it later became known as Gulf War Illness (GWI). Researchers and healthcare professionals since the early 1990s have been working extensively on alleviating the symptoms expressed in GWI as well as attempting to understand the mechanisms behind this illness. Scientific literature as well as reports from GWI veterans indicate that the toxic exposures during deployment may be responsible for the symptoms. These toxic exposures potentially include nerve agents, pyridostigmine bromide pills, pesticides, munitions with depleted uranium, and burning oil well fires. GWI currently affects 25-32% of the 697,000 American troops who were stationed overseas during the short conflict. The purpose of this paper is to review the literature on neurotoxic exposures in Gulf War Illness, to explain how these exposures may lead to glutamate excitotoxicity, which has been implicated in the majority of the symptoms characterizing the illness, and to propose a novel treatment option for GWI.

Molecular mechanisms for the antidepressant-like effects of a low-dose ketamine treatment in a DFP-based rat model for Gulf War Illness.

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Abstract

Exposure to organophosphates (OP) during the First Gulf War is among one of the factors for Gulf War Illness (GWI) development in veterans and it has been challenging to treat GWI symptoms with existing therapies. Ketamine produces a rapid-onset and sustained antidepressant response, but there is no evidence whether ketamine treatment is effective for GWI depression. Repeated, low-dose exposure to diisopropyl fluorophosphate (DFP) mimic Gulf War related OP exposures and produces a chronic depressive state in rats. In this study, DFP-exposed rats treated with ketamine (10 mg/kg, i.p.) exhibited antidepressant-like effect on the Forced Swim Test at 1-h. This effect persisted at 24-h post ketamine, a time-point by which it is eliminated from the brain suggesting involvement of mechanisms that affect long-term synaptic plasticity. Western blot analysis showed significantly lower Brain-Derived Neurotrophic Factor (BDNF) levels in DFP rat brains. Ketamine produced a nonsignificant increase in BDNF expression at 1-h but produced a larger, significant (2.2-fold) increase at 24-h in DFP rats. We previously reported chronic hippocampal calcium elevations ($[Ca^{2+}]_i$) in DFP rats. Ketamine-treated DFP rats exhibited significantly lower $[Ca^{2+}]_i$ at 1-h but not at 24-h. Interestingly, treatment with ANA-12, a TrkB-BDNF receptor antagonist, in DFP rats blunted ketamine's antidepressant-like effect at 24-h but not at 1-h. These experiments suggest that in a rat model of DFP-induced depression, inhibition of the NMDAR-Ca^{2+} contributes to the rapid-onset antidepressant effects of ketamine while the antidepressant actions that persisted at 24-h post ketamine administration involve upregulation of BDNF signaling.

Neuroinflammation in Gulf War Illness is linked with HMGB1 and complement activation, which can be discerned from brain-derived extracellular vesicles in the blood

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Abstract

Cognitive dysfunction and neuroinflammation are conspicuously observed in Gulf War Illness (GWI). We investigated whether brain inflammation in GWI is associated with activation of high mobility group box-1 (HMGB1) and complement-related proteins in neurons and astrocytes, and brain inflammation can be tracked through neuron-derived extracellular vesicles (NDEVs) and astrocyte-derived EVs (ADEVs) found in the circulating blood. We exposed animals to GWI-related chemicals pyridostigmine bromide, DEET and permethrin, and moderate stress for 28 days. We performed behavioral tests 10 months post-exposure and quantified activated microglia and reactive astrocytes in the cerebral cortex. Then, we measured the concentration of HMGB1, proinflammatory cytokines, and complement activation-related proteins in the cerebral cortex, and NDEVs and ADEVs in the circulating blood. Cognitive impairments persisted in GWI rats at 10 months post-exposure, which were associated with increased density of activated microglia and reactive astrocytes in the cerebral cortex. Moreover, the level of HMGB1 was elevated in the cerebral cortex with altered expression in the cytoplasm of neuronal soma and dendrites as well as the extracellular space. Also, higher levels of proinflammatory cytokines (TNFa, IL-1b, and IL-6), and complement activation-related proteins (C3 and TccC5b-9) were seen in the cerebral cortex. Remarkably, increased levels of HMGB1 and proinflammatory cytokines observed in the cerebral cortex of GWI rats could also be found in NDEVs isolated from the blood. Similarly, elevated levels of complement proteins seen in the cerebral cortex could be found in ADEVs. The results provide new evidence that persistent cognitive dysfunction and chronic neuroinflammation in a model of GWI are linked with elevated HMGB1 concentration and complement activation. Furthermore, the results demonstrated that multiple biomarkers of neuroinflammation could be tracked reliably via analyses of NDEVs and ADEVs in the circulating blood. Execution of such a liquid biopsy approach is especially useful in clinical trials for monitoring the remission, persistence or progression of brain inflammation in GWI patients with drug treatment.

Anthrax Protective Antigen 63 (PA63): Toxic Effects in Neural Cultures and Role in Gulf War Illness (GWI).

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Abstract

Protective antigen (PA) 63 (PA63) is a protein derived from the PA83 component contained in the anthrax vaccine. The anthrax vaccine ("Biothrax") was administered together with other vaccines to Gulf War veterans, about 35% of whom later developed a multisymptom disease (Gulf War Illness [GWI]), with prominent neurological/cognitive/mood symptoms, among others. The disease has been traditionally attributed to exposures to toxic chemicals during the war but other factors could be involved, including vaccines received. Of these, the anthrax vaccine is the most toxic. Here, we assessed directly the PA63 toxin's harmful effects on cultured neuroblastoma 2A (N2A) cells with respect to cell spreading, process formation, apoptosis, and integrity of cell membrane, cytoskeleton, and mitochondria. We found that, when added in N2A cultures, PA63 toxin led to decreased cell spreading and cell aggregation, leading to apoptosis. The mechanisms of PA63-induced cell damage included compromised cell membrane permeability indicated by enhanced access of propidium iodide in cells. In addition, signaling pathways leading to organization of N2A cytoskeleton were negatively affected, as both actin and microtubular networks were compromised. Finally, the mitochondrial membrane potential was impaired in specific assays. Altogether, these alterations led to apoptosis as a collective toxic effect of PA63 which was substantially reduced by the concomitant addition of specific antibodies against PA63.

Assessment of Ketamine and Its Enantiomers in an Organophosphate-Based Rat Model for Features of Gulf War Illness.

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Abstract

Approximately 33% of U.S. soldiers from the first Gulf War suffer from a multi-system disorder known as the Gulf War Illness (GWI). GW veterans suffer from a cluster of symptoms that prominently include fatigue and can include mood-related symptoms**.** Compared to traditional antidepressants, ketamine (KET) produces a fast-onset and long-lasting antidepressant response, but assessments of KET for GWI-related depression are lacking. The etiology of GWI is multi-factorial and exposure to organophosphates (OP) during deployment is one of the factors underlying GWI development. Here, male Sprague-Dawley rats were repeatedly exposed to an OP DFP and three months later these rats, when assessed on a battery of rodent behavioral assays, displayed signs consistent with aspects of GWI characteristics. When treated with a sub-anesthetic dose of KET (3, 5, or 10 mg/kg, i.p.), DFP-treated rats exhibited a significant improvement in immobility time, open-arm exploration, and sucrose consumption as early as 1 h and much of these effects persisted at 24-h post-KET injection. KET's stereoisomers, *R*-KET and *S*-KET, also exhibited such effects in DFP rats, with *R*-KET being the more potent isomer. Our studies provide a starting point for further assessment of KET for GWI depression.

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