A role for neuroimmune signaling in a rat model of Gulf War Illness-related pain.

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Abstract

More than a quarter of veterans of the 1990-1991 Persian Gulf War suffer from Gulf War Illness (GWI), a chronic, multi-symptom illness that commonly includes musculoskeletal pain. Exposure to a range of toxic chemicals, including sarin nerve agent, are a suspected root cause of GWI. Moreover, such chemical exposures induce a neuroinflammatory response in rodents, which has been linked to several GWI symptoms in rodents and veterans with GWI. To date, a neuroinflammatory basis for pain associated with GWI has not been investigated. Here, we evaluated development of nociceptive hypersensitivity in a model of GWI. Male Sprague Dawley rats were treated with corticosterone in the drinking water for 7 days, to mimic high physiological stress, followed by a single injection of the sarin nerve agent surrogate, diisopropyl fluorophosphate. These exposures alone were insufficient to induce allodynia. However, an additional sub-threshold challenge (a single intramuscular injection of pH 4 saline) induced long-lasting, bilateral allodynia. Such allodynia was associated with elevation of markers for activated microglia/macrophages (CD11b) and astrocytes/satellite glia (GFAP) in the lumbar dorsal spinal cord and dorsal root ganglia (DRG). Additionally, Toll-like receptor 4 (TLR4) mRNA was elevated in the lumbar dorsal spinal cord, while IL-1β and IL-6 were elevated in the lumbar dorsal spinal cord, DRG, and gastrocnemius muscle. Demonstrating a casual role for such neuroinflammatory signaling, allodynia was reversed by treatment with either minocycline, the TLR4 inhibitor (+)-naltrexone, or IL-10 plasmid DNA. Together, these results point to a role for neuroinflammation in male rats in the model of musculoskeletal pain related to GWI. Therapies that alleviate persistent immune dysregulation may be a strategy to treat pain and other symptoms of GWI.

Exercise modifies glutamate and other metabolic biomarkers in cerebrospinal fluid from Gulf War Illness and Myalgic encephalomyelitis / Chronic Fatigue Syndrome.

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Abstract

Myalgic encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS) and Gulf War Illness (GWI) share many symptoms of fatigue, pain, and cognitive dysfunction that are not relieved by rest. Patterns of serum metabolites in ME/CFS and GWI are different from control groups and suggest potential dysfunction of energy and lipid metabolism. The metabolomics of cerebrospinal fluid was contrasted between ME/CFS, GWI and sedentary controls in 2 sets of subjects who had lumbar punctures after either (a) rest or (b) submaximal exercise stress tests. Postexercise GWI and control subjects were subdivided according to acquired transient postexertional postural tachycardia. Banked cerebrospinal fluid specimens were assayed using Biocrates AbsoluteIDQ® p180 kits for quantitative targeted metabolomics studies of amino acids, amines, acylcarnitines, sphingolipids, lysophospholipids, alkyl and ether phosphocholines. Glutamate was significantly higher in the subgroup of postexercise GWI subjects who did not develop postural tachycardia after exercise compared to nonexercise and other postexercise groups. The only difference between nonexercise groups was higher lysoPC a C28:0 in GWI than ME/CFS suggesting this biochemical or phospholipase activities may have potential as a biomarker to distinguish between the 2 diseases. Exercise effects were suggested by elevation of short chain acylcarnitine C5-OH (C3-DC-M) in postexercise controls compared to nonexercise ME/CFS. Limitations include small subgroup sample sizes and absence of postexercise ME/CFS specimens. Mechanisms of glutamate neuroexcitotoxicity may contribute to neuropathology and "neuroinflammation" in the GWI subset who did not develop postural tachycardia after exercise. Dysfunctional lipid metabolism may distinguish the predominantly female ME/CFS group from predominantly male GWI subjects.

Transcranial Photobiomodulation to Improve Cognition in Gulf War Illness.

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Abstract

Introduction: Approximately 25-30% of veterans deployed to Kuwait, 1990-91, report persistent multi-symptom Gulf War Illness (GWI) likely from neurotoxicant exposures. Photobiomodulation (PBM) in red/near-infrared (NIR) wavelengths is a safe, non-invasive modality shown to help repair hypoxic/stressed cells. Red/NIR wavelengths are absorbed by cytochrome C oxidase in mitochondria, releasing nitric oxide (increasing local vasodilation), and increasing adenosine tri-phosphate production. We investigated whether PBM applied transcranially could improve cognition, and health symptoms in GWI. **Materials and Methods:** Forty-eight (40 M) participants completed this blinded, randomized, sham-controlled trial using Sham or Real, red/NIR light-emitting diodes (LED) applied transcranially. Fifteen, half-hour transcranial LED (tLED) treatments were twice a week (7.5 weeks, in-office). Goggles worn by participant and assistant maintained blinding for visible red. Pre-/Post- testing was at Entry, 1 week and 1 month post- 15th treatment. Primary outcome measures were neuropsychological (NP) tests; secondary outcomes, Psychosocial Questionnaires, including PTSD. **Results:** Primary Analyses (all participants), showed improvement for Real vs. Sham, for Digit Span Forwards ($p < 0.01$); and a trend for Trails 4, Number/Letter Sequencing ($p < 0.10$). For secondary outcomes, Real group reported more improvement on the SF-36V Plus, Physical Component Score ($p < 0.08$). Secondary Analyses included only subjects scoring below norm (50%ile) at Entry, on specific NP test/s. Real and Sham improved at 1 week after 15th treatment; however, at 1 month, only those receiving Real improved further: Digit Span Total, Forwards and Backwards; Trails 4, Number/Letter Sequencing; California Verbal Learning Test-II, long delay free recall; Continuous Performance Test-II, False Alarm Rate; and Color-Word Interference, Stroop, Trial 3, Inhibition; Sham group worsened, toward Entry values. Only those with more post-traumatic stress disorder (PTSD) symptomatology at Entry, receiving Real, continued to have additional PTSD reduction at 1 month; Sham regressed. **Conclusion:** This study was underpowered ($n = 48$), with large heterogeneity at Entry. This likely contributed to significance or trend to significance, for only two of the NP tests (Digit Span Forwards; Trails 4, Number/Letter Sequencing) and only one general health measure, the SF-36V Plus, Physical Component Score. More subjects receiving Real, self-reported increased concentration, relaxation and sleep. Controlled studies with newer, transcranial LED home treatment devices are warranted; this is expected to increase enrollment. **Clinical Trial Registration:** www.ClinicalTrials.gov, identifier: NCT01782378.

Sex-Based Differences in Plasma Autoantibodies to Central Nervous System Proteins in Gulf War Veterans versus Healthy and Symptomatic Controls.

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Abstract

Veterans from the 1991 Gulf War (GW) have suffered from Gulf War illness (GWI) for nearly 30 years. This illness encompasses multiple body systems, including the central nervous system (CNS). Diagnosis and treatment of GWI is difficult because there has not been an objective diagnostic biomarker. Recently, we reported on a newly developed blood biomarker that discriminates GWI from GW healthy controls, and symptomatic controls with irritable bowel syndrome (IBS) and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). The present study was designed to compare levels of these biomarkers between men and women with GWI, as well as sex-specific effects in comparison to healthy GW veterans and symptomatic controls (IBS, ME/CFS). The results showed that men and women with GWI differ in 2 of 10 plasma autoantibodies, with men showing significantly elevated levels. Men and women with GWI showed significantly different levels of autoantibodies in 8 of 10 biomarkers to neuronal and glial proteins in plasma relative to controls. In summary, the present study addressed the utility of the use of plasma autoantibodies for CNS proteins to distinguish among both men and women veterans with GWI and other healthy and symptomatic control groups.

A Pilot Study to Examine Psychological and Neuropsychological Outcomes and a Novel Detoxification Program for Gulf War Illness.

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Abstract

Introduction: Exposures to environmental toxins have been associated with severe health problems for approximately one-quarter of the nearly 700,000 U.S. soldiers who served in the Gulf War between the years 1990 and 1991. Gulf War illness still affects about 30% of Gulf War veterans (GWV), causing reduced psychological wellness and neuropsychological function.

Method and materials: This pilot study used a randomized wait-list control design to explore the feasibility and efficacy of a novel detoxification method for GWV exposed to toxicants such as pesticides, nerve gases, and pyridostigmine bromide. Our study included 32 GWV (67% male), with a mean age of 51 (range: 43-70, SD = 6.97), who participated in a 4- to 5-week treatment that was hypothesized to reduce the reported psychological and neuropsychological symptoms. Psychological measures used included tests given for the evaluation of neurocognitive function, including motor function for a dominant hand with the grooved pegboard test; verbal and visual immediate and delayed memory with the Wechsler Memory Scale III abbreviated subtests; executive function domains of attention, speed, and mental flexibility with trail making test parts A and B and Stroop color and word test. Psychological status was measured using the nine subscales of the Symptom Checklist-90-Revised.

Results: Primary outcomes included between-group differences in self-reported psychological measures and a neuropsychological battery at 7-day and 3-month assessments. Baseline comparison revealed improvements in 16 of 19 psychological and neuropsychological measures at 7-day assessment and that 13 remained stable at 3-month assessment.

Conclusions: We conclude that the detoxification procedure provided improvement in psychological and cognitive function for GWV and that future study is warranted.

Trial registration: ClinicalTrials.gov NCT01672710.

Cognitive behavioral therapy for insomnia in veterans with gulf war illness: Results from a randomized controlled trial

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Abstract

Aims: To examine whether cognitive behavioral therapy for insomnia (CBT-I), delivered by telephone, improves sleep and non-sleep symptoms of Gulf War Illness (GWI).

Main methods: Eighty-five Gulf War veterans (21 women, mean age: 54 years, range 46-72 years) who met the Kansas GWI case definition, the Centers for Disease Control and Prevention (CDC) case definition for Chronic Multisymptom Illness (CMI), and research diagnostic criteria for insomnia disorder were randomly assigned to CBT-I or monitor-only wait list control. Eight weekly sessions of individual CBT-I were administered via telephone by Ph.D. level psychologists to study participants. Outcome measures included pre-, mid-, and post-treatment assessments of GWI and insomnia symptoms, subjective sleep quality, and continuous sleep monitoring with diary. Outcomes were re-assessed 6-months post-treatment in participants randomized to CBT-I.

Key findings: Compared to wait list, CBT-I produced significant improvements in overall GWI symptom severity, individual measures of fatigue, cognitive dysfunction, depression and anxiety, insomnia severity, subjective sleep quality, and sleep diary outcome measures. The beneficial effects of CBT-I on overall GWI symptom severity and most individual GWI symptom measures were maintained 6-months after treatment.

Significance: GWI symptoms have historically been difficult to treat. Because CBT-I, which is associated with low stigma and is increasingly readily available to veterans, improved both sleep and non-sleep symptoms of GWI, these results suggest that a comprehensive approach to the treatment of GWI should include behavioral sleep interventions.

A Pilot Study of Bioenergetic Marker Relationships in Gulf War Illness: Phosphocreatine Recovery vs. Citric Acid Cycle Intermediates

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Abstract

Impaired bioenergetics have been reported in veterans with Gulf War illness (VGWIs), including prolonged post-exercise recovery of phosphocreatine (PCr-R) assessed with [31]Phosphorus magnetic resonance spectroscopy. The citric acid cycle (CAC) is considered the most important metabolic pathway for supplying energy, with relationships among CAC markers reported to shift in some but not all impaired bioenergetic settings. We sought to assess relations of CAC markers to one another and to PCr-R. Participants were 33 VGWIs and 33 healthy controls 1:1 matched on age-sex-ethnicity. We assessed seven CAC intermediates, and evaluated PCr-R in a subset of matched case-control pairs (N = 14). CAC markers did not significantly differ between cases and controls. Relationships of alpha-ketoglutarate to malate, isocitrate, and succinate were strongly significant in cases with materially weaker relationships in controls, suggesting possible shifts in these markers in concert in VGWIs. PCr-R correlated strongly with five of seven CAC markers in controls (succinate, malate, fumarate, citrate, isocitrate, range r = -0.74 to -0.88), but bore no relationship in VGWIs. In summary, PCr-R related significantly to CAC markers in healthy controls, but not VGWIs. In contrast, relations of CAC markers to one another appeared to shift (often strengthen) in VGWIs.

Cause-Specific Mortality Risks Among U.S. Veterans: 25 Years After Their Service in the 1990-1991 Gulf War

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Abstract

Purpose: There is concern about adverse health effects related to military service in the 1990-1991 Gulf War. This study assessed cause-specific mortality risks among Veterans who served in the war.

Methods: The mortality of 621,244 veterans deployed to the Gulf War was compared to that of 745,704 Veterans who served during the war but were not deployed to the Gulf Theater. Cause-specific mortality of both deployed and non-deployed was also compared to that of the US general population.

Results: There was no increased risk of disease-specific mortality among deployed Veterans compared to non-deployed. Deployed Veterans did have an increased risk of motor vehicle deaths compared to non-deployed Veterans, (hazard ratio, 1.12;, 95% confidence interval, 1.04-1.21). Cause-specific mortality of both deployed and non-deployed Veterans was less than that of the US population. When stratified by gender, only female Veterans, both deployed and non-deployed, had increased risks of suicide compared to the female US population (standardized mortality ratio, 1.40; 95% confidence interval, 1.13-1.71 and standardized mortality ratio, 1.22; 95% confidence interval, 1.05-1.40, respectively).

Conclusion: There was no increased risk of disease mortality among Veterans of the 1990-1991 Gulf War. Both deployed and non-deployed female Veterans had increased risks of suicide compared to US female population.

Veterans with Gulf War Illness perceptions of management strategies

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Abstract

Aims: Gulf War Illness (GWI) is a prevalent and disabling condition characterized by persistent physical symptoms. Clinical practice guidelines recommend self-management to reduce the disability from GWI. This study evaluated which GWI self-management strategies patients currently utilize and view as most effective and ineffective.

Materials and methods: Data were collected from 267 Veterans during the baseline assessment of a randomized clinical trial for GWI. Respondents answered 3 open-ended questions regarding which self-management strategies they use, view as effective, and view as ineffective. Response themes were coded, and code frequencies were analyzed.

Key findings: Response frequencies varied across questions (in-use: n = 578; effective: n = 470; ineffective: n = 297). Healthcare use was the most commonly used management strategy (38.6% of 578), followed by lifestyle changes (28.5% of 578), positive coping (13% of 578), and avoidance (13.7% of 578). When asked about effective strategies, healthcare use (25.9% of 470), lifestyle change (35.7% of 470), and positive coping (17.4% of 470) were identified. Avoidance was frequently identified as ineffective (20.2% of 297 codes), as was invalidating experiences (14.1% of 297) and negative coping (10.4% of 297).

Significance: Patients with GWI use a variety of self-management strategies, many of which are consistent with clinical practice guidelines for treating GWI, including lifestyle change and non-pharmacological strategies. This suggests opportunities for providers to encourage effective self-management approaches that patients want to use.

Resolving whether inhalation of depleted uranium contributed to Gulf War Illness using high-sensitivity mass spectrometry

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Abstract

Of the hypothesized causes of Gulf War Illness (GWI), a chronic multi-symptom illness afflicting approximately 25% of military personnel deployed to the 1991 Gulf War, exposure to depleted uranium (DU) munitions has attracted international concern. Past research has not tested the potential association of GWI with inhaled DU nor used isotope mass spectrometry of sufficient sensitivity to rigorously assess prior DU exposure. We applied a standard biokinetic model to predict the urinary concentration and uranium isotopic ratios for a range of inhalation exposures. We then applied sensitive mass spectrometry capable of detecting the predicted urinary DU to 154 individuals of a population-representative sample of U.S. veterans in whom GWI had been determined by standard case definitions and DU inhalation exposures obtained by medical history. We found no difference in the $^{238}U/^{235}U$ ratio in veterans meeting the standard case definitions of GWI versus control veterans, no differences by levels of DU inhalation exposure, and no ^{236}U associated with DU was detected. These findings show that even the highest likely levels of DU inhalation played no role in the development of GWI, leaving exposure to aerosolized organophosphate compounds (pesticides and sarin nerve agent) as the most likely cause(s) of GWI.

Altered hippocampal function and cytokine levels in a rat model of Gulf War illness.

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Abstract

Aims: Gulf War illness (GWI) is a disorder affecting military personnel deployed in the Gulf War (GW) from 1990 to 1991. Here, we will use a rat model of GWI to evaluate hippocampal function and cytokine levels.

Materials and methods: Rats were exposed to diethyltoluamide and permethrin via dermal absorption and pyridostigmine bromide via gavage with or without a 5-min restraint for 28 days. Immediate and delayed effects of GW chemical exposure were evaluated using electrophysiology to quantitate hippocampal function, behavioral tests to assess cognitive effects and biochemical assays to measure neurotransmitter and cytokine levels.

Key findings: Behavioral data revealed a statistically significant increase in motor activity at 3 months following completion of exposures, potentially indicating increased excitability, and/or restlessness. Electrophysiology data revealed statistically significant changes in paired pulse facilitation and input-output function of CA1 hippocampal neurons within 24 h and 3 months following completion of exposures. There was also a statistically significant reduction in the frequency of spontaneous firing activity of hippocampal neurons within 24 h following exposures. Naïve hippocampal slices directly incubated in GW chemicals also resulted in similar changes in electrophysiological parameters. Biochemical measurements revealed reduced hippocampal glutamate level at 3 months post-exposure. Furthermore, there was a statistically significant increase in plasma and hippocampal levels of IL-13, as well as decrease in plasma level of IL-1β.

Significance: Our data support an effect on glutamate signaling within the hippocampus as indicated by changes in PPF and hippocampal level of glutamate, with some activation of T helper type 2 immune response.

Biological measures and diagnostic tools for Gulf War Illness - A systematic review.

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Abstract

Aims: Gulf War Illness (GWI) is a chronic multisymptom illness with debated etiology and pathophysiology. This systematic review catalogues studies of validated biological tests for diagnosing GWI and of associations between biological measures and GWI for their promise as biomarkers.

Main methods: We searched multiple sources through February 2020 for studies of diagnostic tests of GWI and of associations between biological measures and GWI. We abstracted data on study design, demographics, and outcomes. We assessed the risk of bias of included studies.

Key findings: We did not identify any studies validating tests of biomarkers that distinguish cases of GWI from non-cases. We included the best-fitting studies, 32 completed and 24 ongoing or unpublished studies, of associations between GWI and biological measures. The less well-fitting studies (n = 77) were included in a Supplementary Table. Most studies were of the central nervous and immune systems and indicated a significant association of the biological measure with GWI case status. Biological measures were heterogeneous across studies.

Significance: Our review indicates that there are no existing validated biological tests to determine GWI case status. Many studies have assessed the potential association between a variety of biological measures and GWI, the majority of which pertain to the immune and central nervous systems. More importantly, while most studies indicated a significant association between biological measures and GWI case status, the biological measures across studies were extremely heterogeneous. Due to the heterogeneity, the focus of the review is to map out what has been examined, rather than synthesize information.

Ocular manifestations and biomarkers of Gulf War Illness in US veterans.

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Abstract

Gulf War Illness (GWI) is a multisystem disease with variable presentations, making diagnosis difficult. Non-invasive biomarkers would aid in disease diagnosis. We hypothesized that the eye could serve as a biomarker for GWI. We performed a retrospective case-control study using a sample of 1246 patients seen during a 5-month period in an optometry clinic. We identified veterans who were active duty during the Gulf War Era and either had a questionnaire-based diagnosis of GWI (cases) or did not (controls). Medical records were reviewed for eye and medical co-morbidities, medication use, and retinal macular and nerve fiber layer (NFL) thicknesses based on optical coherence tomography (OCT) images. Compared to controls (n = 85), individuals with GWI (n = 60) had a higher frequency of dry eye symptoms (50% vs 32.9%, p = 0.039). Multivariable analysis revealed average retinal NFL thickness (odds ratio; OR = 0.95), cup-to-disc ratio (OR = 0.005), age (OR = 0.82), and PTSD (OR = 20.5) were predictors of a GWI diagnosis. We conclude that GWI is associated with dry eye symptoms and RNFL thinning may serve as a biomarker for disease.