J Pharmacol Exp Ther. **2020 Jan 6**. pii: jpet.119.263053. doi: 10.1124/jpet.119.263053. PMID: 31907304. [Epub ahead of print]

Dorsoventral-specific effects of a sarin surrogate, diisopropylfluorophosphate, on synaptic transmission in the mouse hippocampus.

Brown KA[1], Filipov NM[1], Wagner JJ[2].

Author information:
1. University of Georgia.
2. University of Georgia jwagner@uga.edu.

Abstract

While there has been an increasing appreciation for functional differences between the dorsal (dH) and ventral (vH) hippocampal sectors, there is a lack of information characterizing the cholinergic and noncholinergic mechanisms of acetylcholinesterase inhibitors on synaptic transmission along the hippocampal dorsoventral axis. Diisopropylfluorophosphate (DFP) is an organophosphate (OP) that is commonly employed as a nerve agent surrogate in vitro as well as in rodent models of disease states such as Gulf War Illness. The present study investigated the cholinergic and noncholinergic mechanisms responsible for the effects of acute DFP exposure on dH and vH synaptic transmission in a hippocampal slice preparation. A paired- pulse extracellular recording protocol was utilized to monitor the population spike (PS_1) amplitude as well as the PS paired-pulse ratio (PS-PPR) in the CA1 subfield of the dH and the vH. We observed that DFP-induced PS_1 inhibition was produced by a cholinergic mechanism in the dH whereas a noncholinergic mechanism was indispensable in mediating the inhibitory effect of DFP on the PS_1 in the vH. PS-PPR in both dH and vH sectors was increased by acute DFP exposure, an effect that was blocked by an NMDAR antagonist but not by cholinergic antagonists. Clinical reports have indicated dorsoventral-specific hippocampal abnormalities in cases of OP intoxications. Therefore, the observed dorsoventral-specific noncholinergic mechanisms underlying the effects of DFP on hippocampal synaptic transmission may have important implications for the treatment of OP overexposures. SIGNIFICANCE STATEMENT: It is unknown if acetylcholinesterase inhibitors differentially impact dorsal and ventral hippocampal synaptic transmission. The data in the present study shows that an organophosphate, diisopropylfluorophosphate, impacts glutamatergic transmission along the dorsoventral axis in a hippocampal slice preparation via distinct cholinergic and noncholinergic mechanisms. These findings may provide insight into investigations of therapeutic agents that target noncholinergic mechanisms in cases of organophosphate overexposures.

BMJ Case Rep. **2020 Jan 6**;13(1). pii: e232502. doi: 10.1136/bcr-2019-232502. PMID: 31911410.

Low-dose naltrexone as a treatment for chronic fatigue syndrome.

Bolton MJ[1], Chapman BP[2], Van Marwijk H[3].

Author information:
1. Patient, Manchester, UK.
2. Patient, West Sussex, UK.
3. Department of Primary Care and Public Health, Brighton and Sussex Medical School, Brighton, UK H.vanMarwijk@bsms.ac.uk.

Abstract

Naltrexone is used as an off-label treatment in low doses for several chronic immune-modulated disorders in many countries. Although only small-scale clinical trials have been performed, these suggest efficacy in several diseases including Crohn's disease, fibromyalgia and Gulf War Illness. Despite numerous internet reports of response to low-dose naltrexone (LDN), no clinical trials exist in people with chronic fatigue syndrome. This condition is characterised by chronic profound fatigue, postexertional malaise, pain and autonomic and neurocognitive disturbances. This series of three case reports compiled by people with long-term ill-health due to chronic fatigue syndrome shows the range of responses they observed when taking LDN, from life changing to a reduction in some symptoms only. Treatment doses ranged from 4 to 12 mg. Clinical trials may be warranted to explore the potential use of naltrexone in people with these debilitating illnesses which currently have no licensed treatments available.

Mil Med. **2020 Jan 7**;185(Supplement_1):554-561. doi: 10.1093/milmed/usz299. PMID: 32074351

Towards a Treatment for Gulf War Illness: A Consensus Docking Approach.

Jaundoo R[1,2,3], Bohmann J[4], Gutierrez GE[5], Klimas N[1,3,6], Broderick G[1,2,3,7,8], Craddock TJA[1,2,3,9].

Author information:
1. Institute for Neuro-Immune Medicine, Nova Southeastern University, 3301 College Avenue, Fort Lauderdale, FL 33314-7796.
2. Department of Psychology & Neuroscience, Nova Southeastern University, 3301 College Avenue, Fort Lauderdale, FL 33314-7796.
3. Department of Clinical Immunology, Nova Southeastern University, 3301 College Avenue, Fort Lauderdale, FL 33314-7796.
4. Pharmaceuticals and Bioengineering Department, Southwest Research Institute, 6220 Culebra Road, San Antonio, TX 78238-5166.
5. Pharmaceuticals and Bioengineering, Chemistry and Chemical Engineering Division, Southwest Research Institute, 6220 Culebra Road, San Antonio, TX 78238-5166.
6. Miami Veterans Affairs Medical Center, 1201 N.W. 16th Street, Miami, FL 33125.
7. Rochester Institute of Technology, One Lomb Memorial Drive, Rochester, NY 14623-5603.
8. Centre for Clinical Systems Biology, Rochester General Hospital Research Institute, 100 Kings Highway South, Rochester, NY 14617.
9. Department of Computer Science, Nova Southeastern University, 3301 College Avenue, Fort Lauderdale, FL 33314-7796.

Abstract

INTRODUCTION:

Gulf War Illness (GWI) currently has no known cure and affects soldiers deployed during the Persian Gulf War. It is thought to originate from exposure to neurotoxicants combined with battlefield stress, and previous research indicates that treatment first involves inhibition of interleukin-2 and tumor necrosis factor alpha, followed by the glucocorticoid receptor. However, the off-target effects of pharmaceuticals hinder development of a drug treatment therapy.

MATERIALS AND METHODS:

AutoDock 4.2, AutoDock Vina, and Schrodinger's Glide were used to perform consensus docking, a computational technique where pharmaceuticals are screened against targets using multiple scoring algorithms to obtain consistent binding affinities. FDA approved pharmaceuticals were docked against the above-mentioned immune and stress targets to determine a drug therapy for GWI. Additionally, the androgen and estrogen targets were screened to avoid pharmaceuticals with off-target interactions.

RESULTS:

While suramin bound to both immune targets with high affinity, top binders of the hormonal and glucocorticoid targets were non-specific towards their respective proteins, possibly due to high structure similarity between these proteins.

CONCLUSIONS:

Development of a drug treatment therapy for GWI is threatened by the tight interplay between the immune and hormonal systems, often leading to drug interactions. Increasing knowledge of these interactions can lead to break-through therapies.

Brain Commun. 2020;2(1):fcz039. doi: 10.1093/braincomms/fcz039. PMCID: PMC6989731. PMID: 32025659. Epub **2020 Jan 12**.

Exercise alters cerebellar and cortical activity related to working memory in phenotypes of Gulf War Illness.

Washington SD[1], Rayhan RU[2], Garner R[1], Provenzano D[1], Zajur K[1], Addiego FM[1], VanMeter JW[3], Baraniuk JN[1].

Author information:
1. Department of Medicine, Georgetown University Medical Center, Washington, DC 20057, USA.
2. Department of Physiology and Biophysics, Howard University College of Medicine, Washington, DC 20059, USA.
3. Center for Functional and Molecular Imaging, Georgetown University Medical Center, Washington, DC 20057, USA.

Abstract

Gulf War Illness affects 25-32% of veterans from the 1990-91 Persian Gulf War. Post-exertional malaise with cognitive dysfunction, pain and fatigue following physical and/or mental effort is a defining feature of Gulf War Illness. We modelled post-exertional malaise by assessing changes in functional magnetic resonance imaging at 3T during an N-Back working memory task performed prior to a submaximal bicycle stress test and after an identical stress test 24 h later. Serial trends in postural changes in heart rate between supine and standing defined three subgroups of veterans with Gulf War Illness: Postural Orthostatic Tachycardia Syndrome (GWI-POTS, 15%, $n = 11$), Stress Test Associated Reversible Tachycardia (GWI-START, 31%, $n = 23$) and Stress Test Originated Phantom Perception (GWI-STOPP, no postural tachycardia, 54%, $n = 46$). Before exercise, there were no differences in blood oxygenation level-dependent activity during the N-Back task between control ($n = 31$), GWI-START, GWI-STOPP and GWI-POTS subgroups. Exercise had no effects on blood oxygenation level-dependent activation in controls. GWI-START had post-exertional deactivation of cerebellar dentate nucleus and vermis regions associated with working memory. GWI-STOPP had significant activation of the anterior supplementary motor area that may be a component of the anterior salience network. There was a trend for deactivation of the vermis in GWI-POTS after exercise. These patterns of cognitive dysfunction were apparent in Gulf War Illness only after the exercise stressor. Mechanisms linking the autonomic dysfunction of Stress Test Associated Reversible Tachycardia and Postural Orthostatic Tachycardia Syndrome to cerebellar activation, and Stress Test Originated Phantom Perception to cortical sensorimotor alterations, remain unclear but may open new opportunities for understanding, diagnosing and treating Gulf War Illness.

Toxicology**. 2020 Jan 18**;431:152379. doi: 10.1016/j.tox.2020.152379. PMID: 31962143. [Epub ahead of print]

Multifunctional compounds lithium chloride and methylene Blue attenuate the negative effects of diisopropylfluorophosphate on axonal transport in rat cortical neurons.

Naughton SX[1], Beck WD[1], Wei Z[1], Wu G[1], Terry AV Jr[2].

Author information:
1. Department of Pharmacology and Toxicology, Medical College of Georgia, Augusta University, Augusta, 30912 Georgia.
2. Department of Pharmacology and Toxicology, Medical College of Georgia, Augusta University, Augusta, 30912 Georgia. Electronic address: aterry@augusta.edu.

Abstract

Organophosphates (OPs) are valuable as pesticides in agriculture and for controlling deadly vector-borne illnesses; however, they are highly toxic and associated with many deleterious health effects in humans including long-term neurological impairments. Antidotal treatment regimens are available to combat the symptoms of acute OP toxicity, which result from the irreversible inhibition of acetylcholinesterase (AChE). However, there are no established treatments for the long-term neurological consequences of OP exposure. In addition to AChE, OPs can negatively affect multiple protein targets as well as biological processes such as axonal transport. Given the fundamental nature of axonal transport to neuronal health, we rationalized that this process might serve as a general focus area for novel therapeutic strategies against OP toxicity. In the studies described here, we employed a multi-target, phenotypic screening, and drug repurposing strategy for the evaluations of potential novel OP-treatments using a primary neuronal culture model and time-lapse live imaging microscopy. Two multi-target compounds, lithium chloride (LiCl) and methylene blue (MB), which are FDA-approved for other indications, were evaluated for their ability to prevent the negative effects of the OP, diisopropylfluorophosphate (DFP) on axonal transport. The results indicated that both LiCl and MB prevented DFP-induced impairments in anterograde and retrograde axonal transport velocities in a concentration dependent manner. While in vivo studies will be required to confirm our in vitro findings, these experiments support the potential of LiCl and MB as repurposed drugs for the treatment of the long-term neurological deficits associated with OP exposure (currently an unmet medical need).

Mil Med. **2020 Feb 2**. pii: usz471. doi: 10.1093/milmed/usz471. PMID: 32009157. [Epub ahead of print]

Gulf War Illness Symptom Severity and Onset: A Cross-Sectional Survey.

Fappiano CM[1], Baraniuk JN[2].

Author information:
1. Georgetown University School of Medicine, 3800 Reservoir Road, NW, Washington, DC 20007-2197.
2. Division of Rheumatology, Immunology, and Allergy, Georgetown University, 3800 Reservoir Road, NW, Washington, DC 20007-2197.

Abstract

INTRODUCTION:

Gulf War illness (GWI) affects 25 to 32% of the 693,826 veterans of the First Persian Gulf War. The etiology and pathophysiology of GWI remain controversial, but the condition is attributed to toxic exposures and stress in the deployed setting. The Kansas criteria used for GWI diagnosis highlight 37 symptoms that were more prevalent in deployed compared to nondeployed veterans. This study employed the Kansas criteria to identify recent symptom severity, assess the perceived burden of disease for veterans with GWI, and characterize disease course over the past three decades.

MATERIALS AND METHODS:

The Kansas criteria were operationalized into a questionnaire to provide a summary of symptom severity, approximate year of onset, and an aid for diagnosis. The online version of the questionnaire was completed by 485 veterans with GWI. Symptom data were grouped for analysis based on observed trends. This study received approval from the Georgetown University Institutional Review Board (IRB 2018-0430).

RESULTS:

Symptom severity for the past 6 months demonstrated a high burden of disease for veteran participants. Frequency analysis of total severity scores (out of 148) showed a unimodal distribution with a median score of 95 (1st quartile = 78, 3rd quartile = 110), minimum score of 19, and maximum of 146. Over 89% of respondents had moderate or severe fatigue, sleep disturbances, pain, and abdominal symptoms over the past 6 months. The veterans who participated in this study reported cumulative frequencies higher than those in a meta-analysis of 21 GWI large epidemiologic cross-sectional studies for symptoms around 1998. The cumulative frequency of symptoms indicated long duration of symptoms, although recall bias must be taken into consideration.

CONCLUSIONS:

This cross-sectional sample of self-selected veterans with GWI demonstrates a high current burden of disease and reveals symptom onset patterns. The information from this study can be used to better understand the long-term trajectory of GWI and be integrated into the treatment and diagnosis of impacted veterans. It can also be used as historical deployed health data and inform the future medical care of combat veterans experiencing health effects from war exposures.

Brain Behav Immun. **2020 Feb 3**. pii: S0889-1591(19)31334-0. doi: 10.1016/j.bbi.2020.01.020. PMID: 32027960. [Epub ahead of print]

In-vivo imaging of neuroinflammation in Veterans with Gulf War Illness.

Alshelh Z[1], Albrecht DS[2], Bergan C[1], Akeju O[2], Clauw DJ[3], Conboy L[4], Edwards RR[5], Kim M[1], Lee YC[6], Protsenko E[1], Napadow V[7], Sullivan K[8], Loggia ML[9].

Author information:
1. Department of Radiology, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA.
2. Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.
3. Department of Anesthesiology, Medicine (Rheumatology), and Psychiatry, Chronic Pain and Fatigue Research Center, University of Michigan, Ann Arbor, MI, USA.
4. Department of Medicine, Beth Israel Deaconess Medical Centre, Harvard Medical School, Boston, MA, USA.
5. Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.
6. Division of Rheumatology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA.
7. Department of Radiology, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA; Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.
8. Department of Environmental Health, Boston University School of Public Health, Boston, MA, USA.
9. Department of Radiology, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA. Electronic address: marco.loggia@mgh.harvard.edu.

Abstract

Gulf War Illness (GWI) is a chronic disorder affecting approximately 30% of the veterans who served in the 1991 Gulf War. It is characterised by a constellation of symptoms including musculoskeletal pain, cognitive problems and fatigue. The cause of GWI is not definitively known but exposure to neurotoxicants, the prophylactic use of pyridostigmine bromide (PB) pills, and/or stressors during deployment have all been suspected to play some pathogenic role. Recent animal models of GWI have suggested neuroinflammatory mechanisms may be implicated, including a dysregulated activation of microglia and astrocytes. However, neuroinflammation has not previously been directly observed in veterans with GWI. To measure GWI-related neuroinflammation in GW veterans, we conducted a Positron Emission Tomography (PET) study using [^{11}C]PBR28, which binds to the 18 kDa translocator protein (TSPO), a protein upregulated in activated microglia/macrophages and astrocytes. GWI (n=15) and healthy controls (HC, n=33, including a subgroup of healthy Gulf War veterans, HC_{VET}, n=8), were examined using integrated [^{11}C]PBR28 PET/MRI. Standardized uptake values normalized by occipital cortex signal (SUVR) were compared across groups and against clinical variables and circulating inflammatory cytokines (TNF-α, IL-6 and IL-1β). SUVR were validated against volume of distribution ratio (n=13). Whether compared to the whole HC group, or only the HC_{VET} subgroup, veterans with GWI demonstrated widespread cortical elevations in [^{11}C]PBR28 PET signal, in areas including precuneus, prefrontal, primary motor and somatosensory cortices. There were no significant group differences in the plasma levels of the inflammatory cytokines evaluated. There were also no significant correlations between [^{11}C]PBR28 PET signal and clinical variables or circulating inflammatory cytokines. Our study provides the first direct evidence of brain upregulation of the neuroinflammatory marker TSPO in veterans with GWI and supports the exploration of neuroinflammation as a therapeutic target for this disorder.

Neurotoxicology. **2020 Feb 17**. pii: S0161-813X(20)30028-0. doi: 10.1016/j.neuro.2020.02.006. PMID: 32081703. [Epub ahead of print]

Brainstem Atrophy in Gulf War Illness.

Zhang Y[1], Avery T[2], Vakhtin AA[2], Mathersul DC[2], Tranvinh E[3], Wintermark M[4], Massaband P[5], Ashford JW[2], Bayley PJ[2], Furst AJ[6].

Author information:
1. War Related Illness and Injury Study Center (WRIISC), Veterans Affairs Palo Alto Health Care System, USA. Electronic address: Yu.Zhang@va.gov.
2. War Related Illness and Injury Study Center (WRIISC), Veterans Affairs Palo Alto Health Care System, USA; Psychiatry and Behavioral Sciences, Stanford University School of Medicine, USA.
3. Neuroradiology, Stanford University School of Medicine, USA.
4. War Related Illness and Injury Study Center (WRIISC), Veterans Affairs Palo Alto Health Care System, USA; Neuroradiology, Stanford University School of Medicine, USA.
5. Radiology, VA Palo Alto Health Care System, USA; Radiology, Stanford University School of Medicine, USA.
6. War Related Illness and Injury Study Center (WRIISC), Veterans Affairs Palo Alto Health Care System, USA; Psychiatry and Behavioral Sciences, Stanford University School of Medicine, USA; Neurology and Neurological Sciences, Stanford University, USA; Polytrauma System of Care (PSC), VA Palo Alto Health Care System, USA.

Abstract

BACKGROUND:

Gulf War illness (GWI) is a condition that affects about 30% of veterans who served in the 1990-91 Persian Gulf War. Given its broad symptomatic manifestation, including chronic pain, fatigue, neurological, gastrointestinal, respiratory, and skin problems, it is of interest to examine whether GWI is associated with changes in the brain. Existing neuroimaging studies, however, have been limited by small sample sizes, inconsistent GWI diagnosis criteria, and potential comorbidity confounds.

OBJECTIVES:

Using a large cohort of US veterans with GWI, we assessed regional brain volumes for their associations with GWI, and quantified the relationships between any regional volumetric changes and GWI symptoms.

METHODS:

Structural magnetic resonance imaging (MRI) scans from 111 veterans with GWI (Age = 49 ± 6, 88% Male) and 59 healthy controls (age = 51 ± 9, 78% male) were collected at the California War Related Illness and Injury Study Center (WRIISC-CA) and from a multicenter study of the Parkinson's Progression Marker Initiative (PPMI), respectively. Individual MRI volumes were segmented and parcellated using FreeSurfer. Regional volumes of 19 subcortical, 68 cortical, and 3 brainstem structures were evaluated in the GWI cohort relative to healthy controls. The relationships between regional volumes and GWI symptoms were also assessed.

RESULTS:

We found significant subcortical atrophy, but no cortical differences, in the GWI group relative to controls, with the largest effect detected in the brainstem, followed by the ventral diencephalon and the thalamus. In a subsample of 58 veterans with GWI who completed the Chronic Fatigue Scale (CFS) inventory of Centers for Disease Control and Prevention (CDC), smaller brainstem volumes were significantly correlated with increased severities of fatigue and depressive symptoms.

CONCLUSION:

The findings suggest that brainstem volume may be selectively affected by GWI, and that the resulting atrophy could in turn mediate or moderate GWI-related symptoms such as fatigue and depression. Consequently, the brain stem should be carefully considered in future research focusing on GWI pathology.

Brain Sci. **2020 Mar 2**;10(3). pii: E143. doi: 10.3390/brainsci10030143. PMID: 32131477.

Modeling the Genetic Basis of Individual Differences in Susceptibility to Gulf War Illness.

Jones BC[1], Miller DB[2], Lu L[1], Zhao W[1], Ashbrook DG[1], Xu F[1], Mulligan MK[1], Williams RW[1], Zhuang D[1], Torres-Rojas C[1], O'Callaghan JP[2].

Author information:
1. Department of Genetics, Genomics and Informatics, Department of Pharmacology, University of Tennessee Health Science Center, 71 South Manassas Street, Memphis, TN 38163, USA.
2. Molecular Neurotoxicology Laboratory, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Morgantown, WV 26505, USA.

Abstract

Between 25% and 30% of the nearly one million military personnel who participated in the 1991 Persian Gulf War became ill with chronic symptoms ranging from gastrointestinal to nervous system dysfunction. This disorder is now referred to as Gulf War Illness (GWI) and the underlying pathophysiology has been linked to exposure-based neuroinflammation caused by organophosphorous (OP) compounds coupled with high circulating glucocorticoids. In a mouse model of GWI we developed, corticosterone was shown to act synergistically with an OP (diisopropylflurophosphate) to dramatically increase proinflammatory cytokine gene expression in the brain. Because not all Gulf War participants became sick, the question arises as to whether differential genetic constitution might underlie individual differences in susceptibility. To address this question of genetic liability, we tested the impact of OP and glucocorticoid exposure in a genetic reference population of 30 inbred mouse strains. We also studied both sexes. The results showed wide differences among strains and overall that females were less sensitive to the combined treatment than males. Furthermore, we identified one OP-glucocorticoid locus and nominated a candidate gene-*Spon1*-that may underlie the marked differences in response.

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