A Proton MRS Study of Hippocampal Impairment in Gulf War Syndrome

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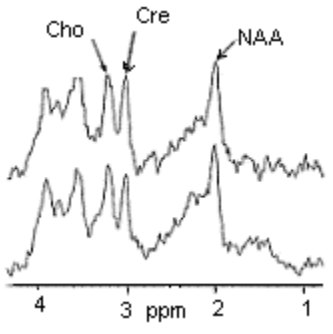
Abstract: Chronic fatigue and/or the effects of exposure to exogenous toxic agents may play a causative role in the Gulf War Syndrome (GWS). Single voxel *in vivo* proton MRS studies of the left and the right hippocampi of veterans were carried out to examine if the hippocampal function is impaired in GWS. The lower NAA/creatine ratio of GWS-veterans (patients) relative to control veterans indicates axonal/neuronal damage and/or loss and suggests a hippocampal dysfunction in GWS.

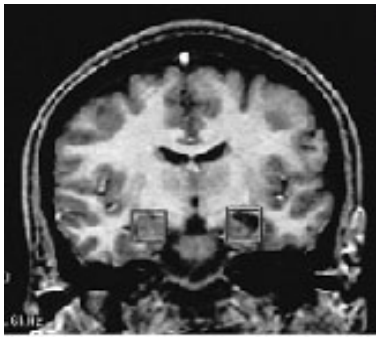
Purpose: Many men and women who served in the Gulf War (GW) military operations during 1990-1991 appear to suffer more frequently from a constellation of symptoms than non-Gulf War veterans. Such ailments (collectively known as the Gulf War Syndrome -- GWS) include depression, difficulty to remember or concentrate, fatigue, headache, irritability, joint pain and stiffness, memory loss, muscle pain, skin rashes and shortness of breath. Data from human and animal model studies exist to suggest that the GWS is a physiologic dysfunction, possibly a combination of chronic fatigue syndrome (CFS) and/or the effects of exposure to exogenous toxic agents (1). Lower than normal levels of cortisol in CFS can lead to less neuroprotection and more inflammation. The head region of hippocampal formation, in particular the granular layer of the dentate gyrus has a dense microvasculature [2] and is vulnerable to the effects of exposure to exogenous toxic agents in circulation. Thus it is interesting to examine if there is any hippocampal dysfunction in GFS.

Methods: Twenty one veterans (17 men and four women; 15 GW and 6 Vietnam-era) between the ages of 31 and 55 years were studied in accordance with approved protocols for human studies. Individuals with a history of seizure disorder, stroke, severe head injury with a loss of consciousness, and uncontrolled medical conditions such as diabetes, chronic hypertension and alcohol or substance abuse were excluded from this study. Five GW- and the six Vietnam-era veterans (all men), who did not report any medical, neurological or psychiatric condition that could interfere with the present study, formed the large control group (N=11). Single voxel PRESS (PROBE-P) proton MR spectra were acquired on a 1.5T (SIGNA, GEMS, Milwaukee) MR imager using a conventional quadrature head coil, a TE of 30 ms, a TR of 3s and 128 FIDs. From orthogonal localizer images, a volume of interest (VOI; typically, 1.5 x 1.5 x 1.5 cc) was chosen anteriorly in the right and left hippocampal regions in tandem for MRS measurements. The spectra were post-processed on a Unix-based data station using SAGE-software (GE Medical Systems) employing zero-filling, an apodization of 1.0 Hz and manual phasing. Each spectrum was computer-fitted with Marquadt-algorithm, and NAA to creatine (NAA/Cre) and choline to creatine (Cho/Cre) ratios were computed for both left and right hippocampal regions of each case. The results were analyzed using a two-factor ANOVA for repeated measure to assess the group or hemispheric differences, and age (i.e., those < the median age of 44.3 yrs. vs. those > 44.3 yrs) and hemispheric status as the covariates.

Results: In vivo proton MR spectra of the left (top) and the right (bottom) hippocampal regions of one study subject and a coronal spoiled GRASS (SPGR) image showing the locations of the VOIs for this case are shown in figures at the bottom of this page. The mean age of GWS patient group (N=10) was significantly lower than that of the larger control group (39.80 ± 6.51 yrs vs. 48.40 ± 6.76 yrs; P = 0.0082) and not statistically different from that of the smaller control group (N = 5) of unaffected GW-veterans. The NAA/Cre ratio of the GWS-group (1.31 ± 0.11) was significantly lower than that of the larger control group (1.43 ± 0.08; $F(1,41) = 9.694$, P < 0.0057) or the smaller control group (1.44 ± 0.10; $F(1,29) = 5.20$, P = 0.04). The mean NAA/Cre ratio of the left side of the GWS group (1.29 ± 0.11) was significantly lower than that of the left (1.42 ± 0.09; P = 0.0083) or the right (1.44 ± 0.08; P = 0.0021) side of the large control group. There was no significant difference in NAA/Cre ratios between the left and right hemispheres of the GWS group or the controls. Within the GWS-, the entire control or the small GW- control group, there was no hemispheric difference for either the NAA/Cre or Cho/Cre ratios. There was no significant difference between the Cho/Cre ratio of the GWS group (1.01 ± 0.13) and the entire control group (1.05 ± 0.11) or the small Gulf War control group (1.08 ± 0.08). The NAA/Cre ratio of the younger group (1.32 ± 0.13; N = 10) was significantly lower than the older group (1.42 ± 0.07; F (1,41) = 6.36; P = 0.0208). There was no statistically significant interaction between younger and older groups or left and right hemispheres.

Discussion: Our findings indicate an axonal and/or neuronal dysfunction or loss and suggest that the hippocampal function may be impaired in GWS. The impairment may have originated from chronic fatigue and/or features specific to the Gulf War only (i.e., the exposure to one or more external agents such as pyridostigmine bromide, DEET, anthrax vaccine, pesticides, mycotoxins, and petroleum gas and smoke).





References:

1. Abou-Donia M.B. et al., *J. Toxicol. Environ. Health* 48, 35-56, 1996; Haley, R.W. and Kurt T.M., *JAMA* 277, 231-238,1997; Kipen H.M.et al., *Arch. Environ. Health* 54 , 313-318, 1999; Meggs. W.J., *Am. J. Epidemiol*. 54, 309-311, 1999; Nicolson, G.L.et al., In: *War and Health* (H. Tapamainen, Ed.) , Zed Press, Helsinki, pp. 431-446, 2002.
2. Y.P. Huang and T. Okudera, *Neuroimag. Clin. N. America* 7, 31-50.1997.