Absolute Quantification of Human Brain Metabolites in Gulf War Syndrome Using Proton MR Spectroscopy at 3T

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Introduction

Gulf War Syndrome (GWS) is an illness reported by combat veterans of the 1991 Persian Gulf War typified by wide-ranging symptoms including chronic fatigue, loss of muscle control, headaches, dizziness and loss of balance, memory problems, muscle and joint pain, indigestion, skin problems, shortness of breath, and insulin resistance. Three distinct GW syndromes have been identified: Syndrome 1 (“impaired cognition”), Syndrome 2 (“confusion-ataxia”), and Syndrome 3 (“central pain”).

Methods

This study included 56 subjects: 12 with Syndrome 1 (Syn1), 17 with Syndrome 2 (Syn2), 12 with Syndrome 3 (Syn3), and 15 control subjects. Single-voxel 1H MRS was performed on a Siemens 3T Trio TIM system with a 12-channel receive-only array head coil, using a conventional PRESS sequence. The acquisition parameters were TR/TE = 2500/30 ms, voxel of size 2×3×2 cm³ placed in left and right basal ganglia, spectral width = 2000 Hz, water suppression bandwidth = 50 Hz, data points = 1024, 96 acquisitions, acquisition time = 4:10 min. A fully relaxed, unsuppressed spectrum was also acquired to measure the water peak (8 averages). Seven metabolite signals (NAA, Cr, choline (Cho), glutamine (Gln), glutamate (Glu), gamma-aminobutyric acid (GABA), and myo-inositol (Ins)) were quantified with AMARES and quantum-mechanically simulated in NMR-SCOPE [6]. The spin Hamiltonian parameters (number of spins, chemical shifts, J-couplings) were obtained from Govindaraju et al [7]. The a priori knowledge was incorporated in the AMARES fitting routines to reduce the number of model parameters and thus to enhance the robustness and speed of the fit.

The absolute metabolite concentrations were calculated using Equation (1). \( C_i \) is the concentration of the metabolite (mM), \( S_i \) is the amplitude of the metabolite and \( S_{SH2O} \) is the signal amplitude of unsuppressed water in the localized spectrum. The terms \( N_i \) and \( N_{SH2O} \) represent the number of \( ^1H \) nuclei contributing to the resonance of metabolites \( i (i = \text{NAA, Cr, Cho, etc.}) \) and water. The parameters \( f_{T1} \) and \( f_{T2} \) are the correction factors for T1 and T2 relaxation times, respectively:

\[ f_{T1} = 1 - \exp(-\text{TR}/T1) \]
\[ f_{T2} = 1 - \exp(-\text{TE}/T2) \]

In this study, the metabolite signals were corrected for T1 and T2 effects according to literature reported values (e.g., The T1 and T2 relaxation times were 1340 ms and 221 ms for NAA, 1320 ms and 145 ms for Cr, and 1180 ms and 217 ms for Cho) [8]. The molar proton concentration of water (\( C_{SH2O} \)) in the brain is assumed to be 45 M.

Results

Spectra with a large water line width (> 0.14 ppm or 18 Hz), low water suppression (< 99%), or obvious artifacts were discarded. On the basis of the criteria, 8 (15%) of 55 spectra in left BG and 2 (4%) of 53 spectra in right BG had unacceptable spectral quality. Short-TE MR spectra acquired on localized volume of interest in MRI normal-appearing basal ganglia of Gulf War veterans are shown in Figure 1. After the T1 and T2 corrections were made, the NAA concentration was significantly lower in basal ganglia in veterans with Syndrome 1 (left, \( P = 0.028 \); right, \( P = 0.008 \)), Syndrome 2 (left, \( P = 0.002 \); right, \( P = 0.028 \)), and Syndrome 3 (left, \( P = 0.313 \); right, \( P = 0.027 \)) than in the control subjects, which is consistent with the findings of the previous study [1], which reported only ratios. In addition, the mean NAA concentration was significantly higher in the left basal ganglia than in the right basal ganglia in all GW syndrome groups, with an overall hemispheric effect significance of \( P < 0.0001 \) (Figure 2).

Discussion

This study represents, to our knowledge, the first in vivo measurements of absolute metabolite concentrations from the basal ganglia in veterans with Gulf War syndrome using 1H MRS. The main observation in this work was the reduction of NAA concentration (-6% for Syndrome 1, -8% for Syndrome 2, and -3% for Syndrome 3) in left BG and in right BG (-6% for Syndrome 1, -6% for Syndrome 2, and -4% for Syndrome 3) of GWS subjects compared to healthy control subjects, significant for Syndromes 1 and 2 in left BG and Syndromes 1, 2, and 3 in right BG. Hence, the present study demonstrated that quantitative in vivo 1H MRS can be used to detect the biochemical abnormalities in brain of GW illness veterans, which may have relevance for the mechanisms of Gulf War syndrome. Our finding supports that the various neurological symptoms reported by Gulf War veterans could be linked to brain injury incurred during the Gulf War.

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