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") [1]. Proton magnetic resonance spectroscopy (^{1}H-MRS) done a decade ago showed that GWS subjects had a significant decrease in N-acetyl aspartate-to-creatine (NAA/Cr) in the pons and basal ganglia [2, 3] and in bilateral hippocampus [4]. More studies are still needed to confirm those observations and to see if the metabolite abnormalities observed in the original studies persist. In this study, *in vivo* brain metabolites in the left and right basal ganglia (BG) of veterans ill with GWS and control veterans were measured by 3T ^{1}H single-voxel spectroscopy (SVS) and quantified by analysis with AMARES using jMRUI software [5].

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 ^{1}H 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 cm^3 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_{H2O} is the signal amplitude of unsuppressed water in the localized spectrum. The terms N_i and N_{H2O} represent the number of ^{1}H nuclei contributing to the resonance of metabolites i(i = NAA, Cr, Cho, etc.) and water. The parameters f_{T1} and f_{T2} are the correction factors for T_1 and T_2 relaxation times, respectively: f_{T1} = 1-exp(-TR/T_1) and f_{T2} = exp(-TE/T_2). In this study, the metabolite signals were corrected for T_1 and T_2 effects according to literature reported values (e.g., The T_1 and T_2 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_{H2O}) in the brain is assumed to be 45 M.

$$[C_i] = \frac{N_{H_2O}}{N_i} \times \frac{S_i}{S_{H_2O}} \times \frac{\left(f_{T_1} \bullet f_{T_2}\right)_{H_2O}}{\left(f_{T_1} \bullet f_{T_2}\right)_i} \times C_{H_2O} \qquad [1]$$

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 T_1 and T_2 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).

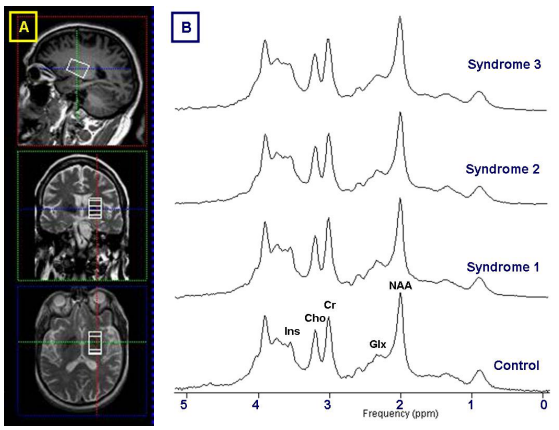

Fig. 1 MR imaging showing the volume of interest (A) and *in vivo* MRS spectra of the left basal ganglia of Gulf War veterans (B).

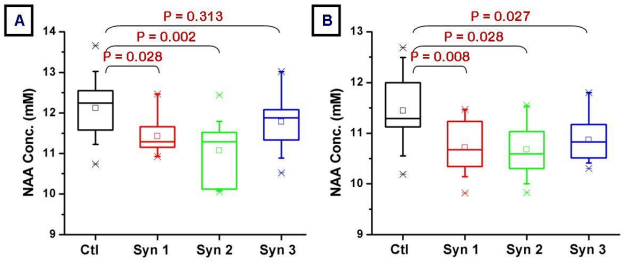

Fig. 2 Absolute NAA concentration (mM) quantified in left (A) and right (B) basal ganglia of Gulf War veteran groups. Data shows mean ± SD for each group using a two tailed *t*-test with significance threshold of P < 0.05.

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 ^{1}H 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* ^{1}H 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.

References

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