Metabolic Abnormality in Early Multiple Sclerosis Observed by Proton MRS

H. E. Möller[1], T. Wetzel[1], M. Tittgemeyer[1,2], S. Hoffmann[1], D. V. Ott[1], C. Preul[1,3], and D. Y. von Cramon[1,2]

[1]Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany, [2]Max Planck Institute for Neurological Research, Cologne, Germany, [3]Department of Neurology, University Hospital Jena, Jena, Germany

Indroduction

Previous research has demonstrated subtle alterations of the normal-appearing white matter (NAWM) in multiple sclerosis (MS) patients with diffusion or magnetization-transfer imaging. Metabolic abnormality related to disease was also evident in MRS examinations. The present longitudinal study focused on the investigation of NAWM by ^{1}H MRS in early MS in single voxels containing minimal perilesional tissue.

Methods

32 patients (f 27, m 5, age 33.6±8.4 y) with early MS (relapsing/remitting 23, clinically isolated syndrome 9; mean disease duration 2.48 y; mean EDSS score 2.36) and 15 healthy control subjects (f 11, m 4, age 28.7±2.7 y) were included in our study. ^{1}H PRESS (*TR* 5 s, *TE* 30 ms, 128 acq.) spectra were acquired at 3 T (Siemens MAGNETOM Trio) from 3-mL voxels located in the fronto-parietal NAWM. Typically 3–4 spectra were recorded in separate sessions from each subject every 6 or 12 months using an 8-channel array head coil. Metabolite concentrations were estimated using LCModel [1] and the unsuppressed water signal as a concentration reference. Spectra with significant artifacts in the residuals or a linewidth (full width at half height, FWHH) exceeding 0.08 ppm were discarded. Concentration estimates with Cramer-Rao lower bounds above 50% were excluded from the statistical analysis (*t*-tests) [2].

Results and Discussion

81 patient and 42 control spectra were recorded with sufficient quality (Fig. 1). Quantitative analysis (Tab. 1) yielded concentrations of total *N*-acetylaspartate (tNAA), total creatine (tCr), total choline (tCh), and myo-inositol (mI) within the normal range. Lactate (Lac) appeared to be significantly elevated in the patients although the concentration estimates typically remained below 1 mM. A significantly decreased level of glutamate plus glutamine (Glx) contrasts with previous reports of normal [3] or elevated [4] glutamate (Glu). It remains to be shown if such discrepancies are related to the disease duration, which was considerably shorter in our study. The reduction in Glx was due to a progressively decreased Glu level in the patients (Fig. 2) whereas glutamine (Gln) appeared unchanged. Additional analysis of individual contributions to tNAA yielded normal *N*-acetylaspartate (NAA) but significantly elevated *N*-acetylaspartylglutamate (NAAG) consistent with previous observation [3].

NAAG is the most abundant peptide neurotransmitter and is thought to have a neuroprotective effect by its ability to activate the metabotropic glutamate receptor mGluR3 [5]. As mGluR3 receptors have been shown to negatively modulate Glu release, we may speculate that the observed decreased Glu is coupled to the increase in NAAG. Extracellular NAAG is hydrolyzed by NAAG peptidase to produce NAA and Glu. Thus, a decline in peptidase activity might also correlate NAAG elevation with reduced Glu. Finally, there is evidence that NAAG can block long-term potentiation (LTP), which might interfere with spatial memory [6].

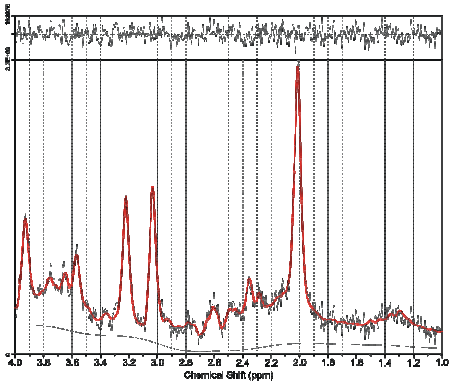

Figure 1. NAWM spectrum (LCModel fit) from a 24-year-old female patient.

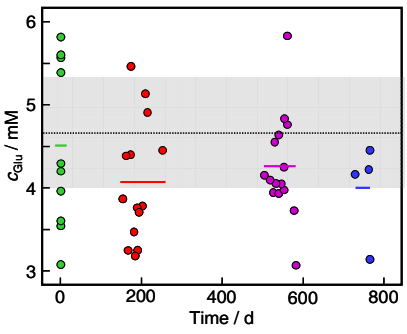

Figure 2. Glu concentrations in the patient group as a function of time. The normal range is indicated in gray.

Table 1. Metabolite concentrations in mM (mean ± SD).

Metabolite	Control group	Patient group
Lac	0.77 ± 0.18	0.93 ± 0.24†
tNAA	7.92 ± 0.75	8.24 ± 1.02
NAA	7.00 ± 0.36	6.92 ± 0.60
NAAG	1.14 ± 0.48	1.58 ± 0.63‡
Glx	6.12 ± 0.91	5.64 ± 0.98†
Glu	4.66 ± 0.64	4.23 ± 0.75*
Gln	1.76 ± 0.64	1.89 ± 0.42
tCr	4.56 ± 0.45	4.50 ± 0.40
tCh	1.43 ± 0.28	1.41 ± 0.18
mI	2.96 ± 0.45	2.94 ± 0.64
FWHH/Hz	5.2 ± 1.3	5.8 ± 1.3
SNR	18.6 ± 3.3	17.4 ± 2.5

*P < 0.05; †P < 0.01; ‡P < 0.001

Conclusions

In patients with early MS, abnormal NAAG was found in the NAWM without indications of axonal damage or elevated glia-cell numbers (normal NAA and mI, respectively). Further research is warranted to investigate the role of altered NAAG levels in MS and a potential role in dysregulation of neurotransmission.

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References. **[1]** S.W. Provencher, *Magn. Reson. Med.* 30: 672 (1993); **[2]** R. Kreis, *NMR Biomed.* 17: 361 (2004); **[3]** H. Vrenken, *Magn. Reson. Med.* 53: 256 (2005); **[4]** R. Srinivasan, *Brain* 128: 1016 (2005) ; **[5]** J.T.. Coyle, *Neurobiol. Dis.* 4: 231 (1997) ; **[6]** J. Neale, *J. Neurochem.* 128: 443 (2000).