Pathobiochemistry of brain damage in multiple sclerosis: Changes in choline and creatine compounds measured by 1H and 31P MRSI

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Introduction

In vivo proton MR spectroscopic imaging (^{1}H MRSI) revealed increases in total creatine (tCr), total choline (tCho) and myoinositol (MI) for brain tissue of patients with multiple sclerosis (MS) (for review see: Richards, Am.J.Roentgenol. 1999). However, pathobiochemical mechanisms related to these changes are still unclear. To evaluate the role of the phosphorylated components contributing to the increase (i.e. phosphocreatine (PCr), glycerophosphocholine (GPE), and phopshocholine (PCho)), we performed a study combining ^{1}H MRSI and ^{1}H-decoupled phosphorus (^{31}P) MRSI.

Methods

Combined ^{1}H and ^{31}P MRSI data were obtained at 3T in 22 MS patients (median age 37.5 years, range 24-57) and in 23 healthy controls (median 35 years, range 23-57) using a double tuned ^{1}H/^{31}P volume head coil (Rapid Biomedical, Würzburg, Germany). 17 patients had relapsing-remitting MS, 4 secondary progressive MS, and one had a clinical isolated syndrome. For ^{1}H MR spectroscopy, an axial 2D MRSI slice was recorded (TR 1500 ms, TE 30 ms and 2 acquisitions) at the level of the centrum semiovale. For ^{31}P MR spectroscopy, a 3D MRSI sequence with WALTZ4 proton decoupling and a flip angle of 60° was used (TR 2000 ms, TE 2.3 ms, 10 acquisitions). As indicated in Fig. 1, in plane grid size was 5 x 5 mm^2 for ^{1}H data and 15 x 15 mm² for ^{31}P data. MRSI data were aligned with structural MRI allowing partial volume corrections for CSF and evaluation of lesion load for the region of interest (ROI). Concentrations of compounds contributing to the tCr and tCho signals were calculated from signal intensities obtained for each modality performing appropriate corrections and calibrations. In addition the residual choline (rCho) and unphosphosphorylated creatine (Cr) were calculated according to: (1) [residual choline] = [tCho]-[PCho]-[GPE] and (2) [Cr] = [tCr]-[PCr].

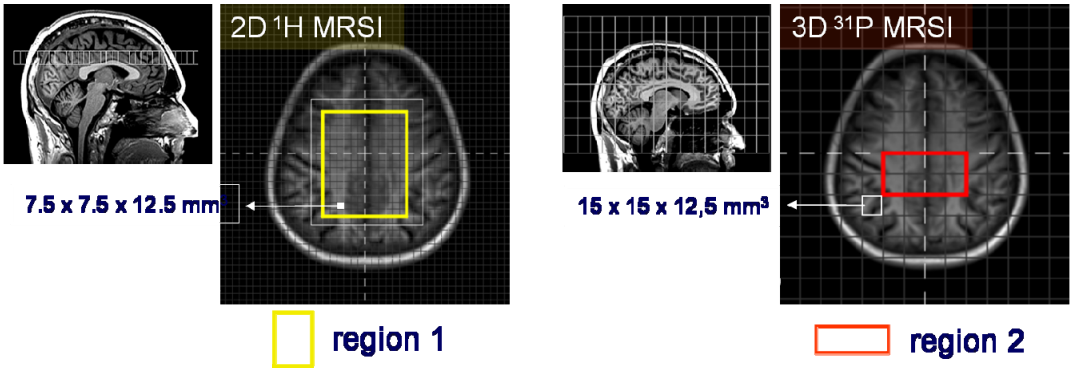

Fig.1: The grids represent the resolution of the ^{1}H MRSI (a) and ^{31}P MRSI (b) data. The yellow frame in (a) marks the entire target region (**region 1**) from which voxels were selected to analyse changes in ^{1}H metabolites. The red frame in (b) marks the **region 2** which includes voxels adjacent to the central sulcus. Changes of ^{31}P and calculated metabolites were evaluated from this region to avoid contamination by other than brain tissue.

Results

In voxels with a lesion fraction >2% the metabolites MI ($p < 0.001$), tCho ($p = 0.014$) were increased and tNAA ($p = 0.008$) was decreased compared to controls. In lesion-free voxels (lesion fraction <2%) MI ($p = 0.002$) and tCr ($p = 0.035$) were increased. Increase in tCr was attributed to equal changes in the phosphorylated and unphosphorylated components (Fig. 2, upper panel). The concentrations of the putative glial markers tCr and MI in lesion-free ^{1}H-MRSI voxels correlated with the global lesion load. No significant difference between patients and controls could be detected for PCho and GPC, however, the difference, i.e. rCho, was increased in patients ($p = 0.058$, lower panel in Fig.2).

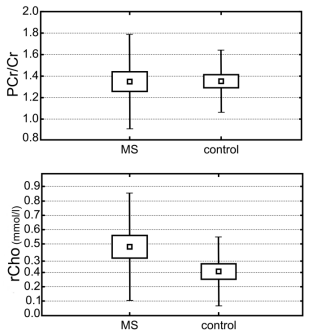

Fig.2: PCr/Cr and residual Choline (rCho) for controls and patients (region2)

Conclusion

Changes in tCr are not related to changes in energy metabolism but rather indicate gliosis. Together with the increase in MI, tCr can be considered as a biomarker for disease severity. A significant tCho increase was mainly due to tCho components not visible by ^{31}P MRS. The origin of this residual choline fraction remains to be investigated.