Global and regional brain concentration of intra- and extra- cellular sodium in MS: a 7 Tesla MRI study

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PURPOSE: It has been demonstrated that the accumulation of intra-axonal sodium ions represents a key factor in the degenerative process occurring in multiple sclerosis (MS)[1] and that partial blockade of sodium channels protects axons from degeneration in experimental models of MS. Our and other groups have shown the feasibility of the measurement of total sodium concentration (TSC) by means of single quantum (SQ) sodium MRI in patients with clinically isolated syndrome[2], relapsing-remitting and progressive multiple sclerosis[3,4]. However, TSC is an average of extra- and intra-cellular sodium concentration (ISC) and SQ sodium MRI does not allow discrimination between the two concentrations. Therefore, we have implemented a new MR pulse sequence for the acquisition of triple quantum (TQ) sodium MRI[5] to assess ISC and intracellular sodium volume fraction (ISVF), an indirect measure of extra-cellular sodium concentration. Due to the low sensitivity of sodium MRI and the low brain ISC, 7 T MRI is particularly suited for the application of this method. The aims of our study were to: 1) measure global and regional brain TSC, ISC and ISVF in MS patients; 2) assess the relationship between brain TSC, ISC and ISVF and lesion and brain volumes; 3) evaluate the relationship between brain TSC, ISC and ISVF and clinical impairment. Target audience: clinicians and MRI physicists interested in gaining insight into the pathogenesis of neurodegeneration in MS

METHODS: Nineteen patients with relapsing-remitting MS (11F; mean age: 40.0±11.2; median EDSS: 2.0, range:0.0-5.5) and 17 age and gender matched CTRLs (8F; mean age: 46.2.0±11.2) underwent MRI at 7 and 3 Tesla (Siemens Medical Solutions). SQ and TQ sodium images were obtained at 7 T by using a modified 3D gradient radial echo sequence with a new 12-step phase-cycling triple-quantum-filtered scheme[5].The 3T MRI protocol included i) double echo–turbo spin echo (TR/TE=5000/11 ms; 48 3-mm thick contiguous axial slices) ii) 3D-T1 MPRAGE (TR/TE/TI=2400/2.71/900 ms; flip spatial resolution= 1 mm^3). TSC, ISC and ISVF maps were created as described in Fleysher et al.[5].Both histogram analysis of global white and gray matter (WM and GM) and voxel-based analysis (SPM8) were used for the measurement of TSC, ISC and ISVF. ANCOVA test controlling for age, gender and intra-cranial volume (significant for $p<0.01$) was used for between-group comparison of TSC, ISC and ISVF values. Differences WM and GM fractions were determined within each group by using an ANOVA test Bonferroni corrected for repeated measures (significant at $p<0.002$).

RESULTS: Compared to CTRLs, MS patients showed higher global GM and WM TSC ($p<0.05$) and lower global ISVF ($p<0.01$). GM and WM ISC were higher in patients than controls but the difference was not statistically significant ($p>0.1$). At the GM voxel-based analysis, TSC was higher in bilateral thalamus, bilateral claustrum, left caudate, bilateral anterior cingulate gyrus, right posterior cingulate gyrus, bilateral frontal middle gyrus, left insula, bilateral precentral gyrus, right postcentral gyrus, left superior and middle temporal gyrus ($p<0.001$ Ke=20, family wise error corrected $p<0.05$). Within each TSC cluster, ISVF was significantly lower in bilateral thalamus, bilateral anterior cingulate gyrus, right posterior cingulate gyrus, bilateral frontal middle gyrus, left insula, bilateral precentral gyrus, right postcentral gyrus, left middle temporal gyrus ($p<0.05$, Ke=10) whereas ISC was significantly higher in bilateral thalamus, bilateral frontal middle gyrus, left insula, bilateral precentral gyrus ($p<0.05$, Ke=10).WM TSC was higher in left inferior fronto-occipital fasciculus, bilateral superior longitudinal fasciculus, bilateral cortico-spinal tract, forceps minor, cingulate gyrus right ($p<0.001$ Ke=20, family wise error $p<0.05$). Within each TSC cluster, ISVF was significantly lower in all the above mentioned tracts ($p<0.05$, Ke=10) whereas ISC was significantly higher in bilateral superior longitudinal fasciculus, left cortico-spinal tract and forceps minor ($p<0.05$, Ke=10). We found an inverse correlation between GM ISVF and EDSS ($r=-0.47$, $p=0.054$) and a direct correlation between GM ISC and WM T2-LV ($r=0.50$, $p<0.05$).

DISCUSSION: Since TSC represents the weighted average of extracellular and intracellular sodium in the examined tissue, the increased value observed in patients with MS could reflect both an increase of extracellular space due to vasogenic oedema and/or cell loss and demyelination as well as an increase of the intracellular sodium due to inflammatory-related over-expression of cellular membrane sodium channels and/or hypercellularity. Our results suggest that TSC increase is mostly due to increase of extracellular sodium concentration (decreased ISVF) and to a lesser extent to increase of ISC. While TSC increase and ISVF decrease in GM could reflect cellular loss, the higher ISC detected in the WM might be explained by the increased influx of sodium in demyelinated axons. The association with EDSS seems to suggest that ISVF is a correlate of cell loss, while ISC is a correlate of the adaptive, compensatory increased intracellular influx of sodium ions. Longitudinal studies are needed to investigate whether ISC is a predictive factor of short- and long-term clinical outcome.

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