Sodium mapping in focal cerebral ischemia in the rat by quantitative ^{23}Na MRI

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INTRODUCTION

Recently, we proposed ^{23}Na MRI as a means to determine precisely the stroke onset time for establishing patient eligibility for thrombolytic therapy (1). However, absolute sodium concentration mapping in rat cerebral ischemia has not been addressed in earlier studies, although these studies have shown agreement between $[Na^+]_{br}$ values measured by ^{23}Na MRI and ^{22}Na radionuclide dilution assay in a whole normal rat brain and in a rat glioma model (2,3) using hour-long imaging times. To establish $[Na^+]_{br}$ as a potential MRI biomarker in evolving focal ischemic stroke with a broad range of $[Na^+]_{br}$ values, ^{23}Na MRI should be performed within several minutes and quantitated over small regions. The present work was undertaken to validate and calibrate ^{23}Na MRI as a quantitative technique with temporal resolution of 5.3 min and precisely targeted very small ROIs in selected brain structures using a gold standard technique, emission flame photometry.

METHODS

Seven normally fed male Sprague-Dawley rats weighing 300 ± 16 g underwent the middle cerebral artery occlusion (MCAO) by an intraluminal suture (4). For ^{23}Na/^{1}H MRI, the animal's head was positioned inside a 5-cm-diameter, 5-cm-long dual-tuned dual-quadrature birdcage transmit/receive RF coil (5). Calibration standards (0-154 mM NaCl) were placed next to animal's head. Images were obtained on a 3 T GEMS scanner. ^{1}H diffusion-weighted multislice spin-echo images (diffusion weighting *b*-factor values of 0, 79, 314, and 707 s/mm^2) were used for reconstruction of ADC maps. For ^{23}Na MRI, a 3D twisted projection imaging (TPI) scheme (6) with a voxel size of 0.48 mm^3 was applied. Every 5.3 min, eight transients were acquired for each of 398 projections using TR/TE of 100/0.4 ms. The inhomogeneity correction of the B_1 field was performed by RF mapping (7). After MRI, Na content in 12-18 0.5-mg brain samples was determined by emission flame photometry at 589 nm. The 40-µm thick coronal brain sections taken every 400 µm at different levels from bregma were digitized and registered to render volumetric reconstructions of the brain. MR and histological 3D images were aligned and analyzed in AMIDE (8). ROIs in the MR images were placed at the positions of punch holes (Fig. 1).

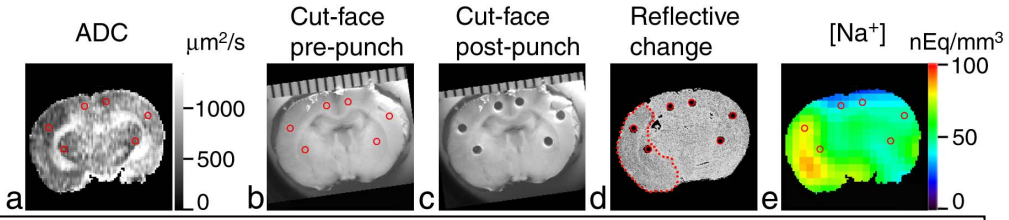

Fig. 1. ROI analysis of Na^+ content in a rat brain after MCAO. Coronal images of the brain (at bregma – 2 mm) are shown. (a) ADC map used to guide the sampling. Ischemic regions in the ipsilateral hemisphere (left-hand side of the image) have (ADC < 550 µm^2/s). (b) Cut-face photographs of the brain in the cryostat before sampling and (c) after sampling showing punch holes. A millimeter scale is shown at the top. (d) Cross-section of the 3D reconstruction of the brain. The change in surface reflectivity of ischemic tissue shows the infarct location (outlined by a red dotted line). Cylindrical ROIs (shown in red) were placed over the punch holes. (e) ^{23}Na MRI at 4.3 hours after MCAO. The calibration standards are external to the rat head and not shown.

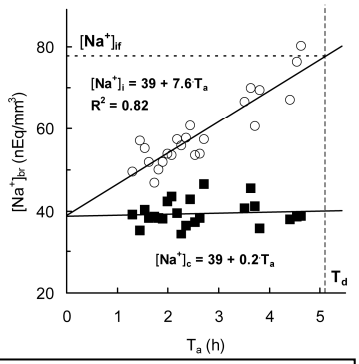

Fig. 2. ^{23}Na MRI intensity in the subcortical ischemic ROI ($[Na^+]_i$, circles) and contralateral normal ROI ($[Na^+]_c$, squares). T_a, time after MCAO; T_d, decapitation time; $[Na^+]_{if}$, estimated $[Na^+]_{br}$ value in the ischemic ROI at the end of the experiment.

RESULTS

Key features of the MRI protocol included the ultra-short TE (0.4 ms) to minimize a quantitation bias caused by the ^{23}Na fast biexponential relaxation, the B_1 mapping to correct for RF inhomogeneities, and the use of calibration standards. The feasibility of ^{23}Na MRI comparison against the gold standard, emission flame photometry, hinged upon two crucial advances in the present study: 1) precise directed sampling of normal and ischemic cortex and caudate putamen, and 2) alignment of MR images with a 3D reconstruction of the punched brain for precise ROI placement. The changes in ^{23}Na signal intensity after MCAO were analyzed in the ipsilateral and homotopic contralateral frontal cortex, parietal cortex and caudate putamen (Fig. 1). In agreement with earlier studies (1,9), ^{23}Na MRI intensity showed a linear increase in ischemic brain and no statistically significant changes in contralateral ROIs over time (Fig. 2). To estimate $[Na^+]_{br}$ in ipsilateral ROIs at the end of the experiment, ^{23}Na image intensities were extrapolated to the decapitation time using linear regression, as shown in Fig. 2. The agreement between the two techniques were assessed using the Bland-Altman plot (10). The plot in Fig. 3 shows a good agreement between ^{23}Na MRI and flame photometry data. The mean value of the relative difference between flame photometry and MRI results (mean bias) and 95% limits of agreement (at ±1.96 SD) were -4% ± 42% of average, and 95% confidence intervals were ±4% of average for the mean bias and ±7% of average for the upper and lower limits of agreement. The mean bias of -4% of average is close to zero, and difference values do not show any systematic variation over the range of measurement (Fig. 3).

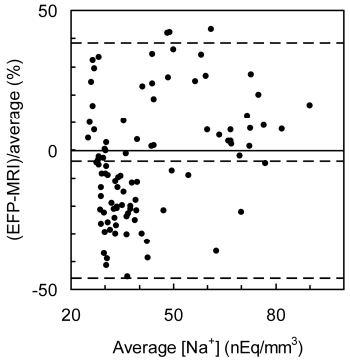

Fig. 3. Bland-Altman analysis of agreement between ^{23}Na MRI and emission flame photometry (EFP). Abscissa is an average (EFP+MRI)/2; ordinate is the difference plotted as percentage of the averages. Dashed horizontal lines represent mean bias and 95% limits of agreement). Data for all animals are combined.

CONCLUSION

The results of this study present a first documented validation of the absolute quantitation of distribution and accumulation of sodium in ischemic rat brain by ^{23}Na MRI. Despite the technical limitations associated with small voxel sizes in a small animal model, ^{23}Na MRI provides accurate and reliable results in the rat model within the whole range of $[Na^+]_{br}$ in ischemia, suggesting that the accuracy would further improve in the clinical setting.

REFERENCES

1. Jones SC, Kharlamov A, Yanovski B, et al. Stroke 2006;37:883-888.
2. Christensen JD, Barrere BJ, Boada FE, Vevea JM, Thulborn KR. Magn Reson Med 1996;36:83-89.
3. Thulborn KR, Davis D, Adams H, Gindin T, Zhou J. Magn Reson Med 1999;41:351-359.
4. Belayev L, Alonso OF, Busto R, Zhao W, Ginsberg MD. Stroke 1996;27:1616-1622.
5. Shen GX, Boada FE, Thulborn KR. Magn Reson Med 1997;38:717-725.
6. Boada FE, Gillen JS, Shen GX, Chang SY, Thulborn KR. Magn Reson Med 1997;37:706-715.
7. Boada FE, Gillen JS, Noll DC, Shen GX, Chang SY, Thulborn KR. Int J Imaging Syst Technol 1997;8:544-550.
8. Loening AM, Gambhir SS. Mol Imaging 2003;2:131-137.
9. Yushmanov VE, Kharlamov A, Boada FE, Jones SC. Magn Reson Med 2007;57:494-500.
10. Bland JM, Altman DG. Stat Methods Med Res 1999;8:135-160.

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