Chemical Shift Sodium Imaging of the Rat Brain during TmDOTP^{5-} Infusion

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Introduction

Long term changes in the intracellular sodium concentration occur in many diseases leading to cell death or cell proliferation [1]. The separation of the total tissue sodium concentration into extra- and intracellular contribution therefore is of considerable interest. The paramagnetic lanthanide chemical shift agent TmDOTP^{5-} produces a large hyperfine shift, which allows for distinction of the resonances from intra- and extracellular sodium ions in perfused organs [2,3]. In the ongoing work TmDOTP^{5-} was used in chemical shift imaging (CSI) experiments and the technique is applied to an animal model of stroke. The aim in this study was to detect the opening of the blood brain barrier (BBB) after stroke and to measure the sodium increase after middle cerebral artery occlusion (MCAo) simultaneously.

Methods

Measurements were performed on a 9.4 T Biospec 94/20 USR (Bruker, Germany) small animal system equipped with 740mT/m gradients. A 105 MHz surface resonator element with variable tuning was used. Inductive coupling was achieved via a longitudinally displaceable coupling loop, which was mounted above the surface coil. Presented datasets were acquired with a 3D acquisition-weighted CSI sequence [4]. Signal was excited with a block pulse of 25µs duration and the phase encoding duration was 320µs leading to a total acquisition delay of 333µs. TR was 50ms, the Ernst angle was estimated with a preliminary Singlepulse experiment with equal TR excitation pulse.

Phantom: To demonstrate the principle of the CSI experiment in combination with the chemical shift agent, a phantom was scanned consisting of two identical vials filled with 0.9% saline solution (Fig.1c). The right vial was additionally doped with 10mM TmDOTP^{5-} (Macrocyclics, USA). CSI parameters: 7 averages, FOV=3x3x5cm^3, matrix=16x16x16. Reconstruction of the data was done with Matlab R2007b. The time dimension of each k-space value, exemplarily shown in Fig.1a for the k-space center, was Fourier transformed to the frequency domain (Fig.1b). The shifted and the unshifted peak were integrated separately and the resulting 3D-dataset was Fourier transformed in the spatial dimensions.

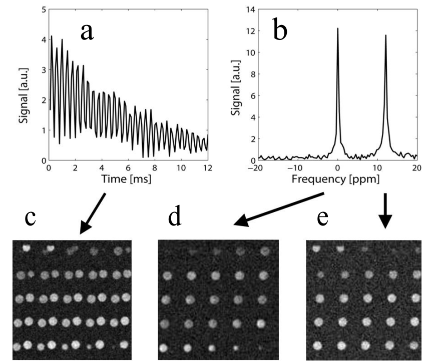

Figure 1: CSI phantom measurements. The phantom consists of two vials filled with saline solution. The right vial was additionally doped with 10mM TmDOTP^{5-}.

Stem cells: Approximately 8 Mio lipo-aspirate-derived mesenchymal stem cells were harvested, washed in PBS buffer, dissolved in contrast media (1-2ml,10mM TmDOTP^{5-}) in an Eppendorf tube and measured with a global Singlepulse sequence (100 averages, TR=300ms) 24h after having solved the cells in TmDOTP^{5-}.

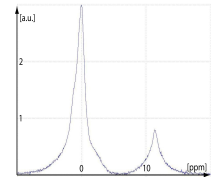

Figure 2: Spectrum of stem cells, dissolved in 10 mM TmDOTP^{5-} solution.

In vivo: Two male Wistar rats weighing 300 to 350g were scanned, one 24h after MCAo induced by the intraluminal filament occlusion technique and one untreated control rat. 2ml of 350mM solution of TmDOTP^{5-} were infused into the tail vein of both rats at an infusion rate of 0.8ml/h which results in a delivered dose of TmDOTP^{5-} of ~1.8mM/kg. The control rat was measured with 47600 encoding steps (eight averages) with 480 spectroscopic data points each. The acquisition time was 40min. A matrix size of 53x43x15 was used, corresponding to a matrix size of 32x28x10 in a non-weighted acquisition case [4]. The field of view was 3.4x2.8x3.0cm^3 leading to a spatial resolution of 1x1x3mm^3. The stroke rat was scanned with more optimized geometrical parameters: FOV=2.1x2.1x3.2cm^3, matrix=33x33x25 corresponding to 21x21x16 (non-weighted), resolution 1x1x2mm^3, 49392 encoding steps (12 averages), acquisition time = 41min.

Results

Phantom: TmDOTP^{5-} increased the resonance frequency of sodium in the right vial by more than 10ppm. By separate integration of two peaks, the total sodium signal, contributing to the slices shown in Fig.1c. splits up into not shifted signal contributions (Fig.1d) andl contributions that are shifted by the contrast agent (Fig.1e). The peak broadening caused by the contrast agent was small compared to the induced shift and therefore no false signal contributions from the complementary vial can be seen in both cases.

Stem cells: 24 hours after having solved the stem cells in 10mM TmDOTP^{5-}, the spectrum still consists of two peaks, one shifted by more than 10ppm.

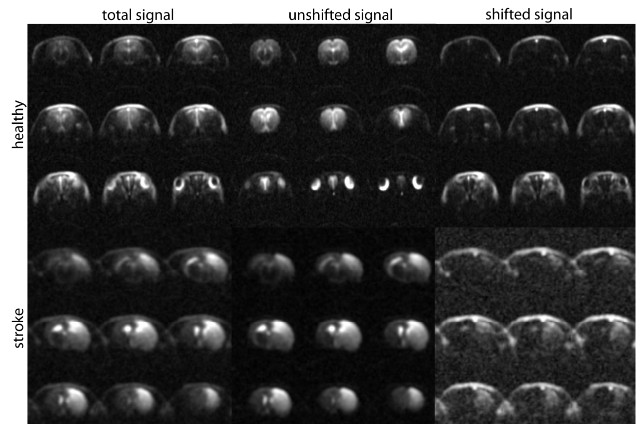

Figure 3: In vivo CSI measurements after TmDOTP^{5-} administration. The upper row shows a untreated control rat, the lower row shows a rat with permanent MCAo.

In vivo: The delivered TmDOTP^{5-} dose shifted parts of the total sodium signal of the healthy rat (Fig.3 upper row) by approximately 4ppm and therefore the distinction between unshifted and shifted sodium compartments was possible. Outside the brain, both signal compartments were detected whereas in the brain nearly the complete signal remained unshifted. The infarcted region of the rat, measured 24 hours after MCAo (Fig.3 lower row), clearly appeared hyperintense in the total sodium image. The unshifted sodium signal was increased in the same regions. Unlike the healthy control rat, infarcted parts of the brain contributed to the shifted sodium signal. However, the shifted regions were smaller than the hyperintense area of the total sodium signal.

Discussion

The presented work demonstrates the feasibility of the CSI sequence in combination with TmDOTP^{5-} to separate signal components of TmDOTP^{5-} surrounding sodium ions of the total sodium signal. In addition, the stem cell measurements demonstrate, that TmDOTP^{5-} does not cross the cell membrane in the time range of MR experiments (<24 h). The fact that no signal compartments were shifted in the untreated brain indicates that the contrast agent did not cross the BBB. However, the stroke experiments lead to the assumption that the BBB was disrupted in parts of the infarcted regions, but the main signal increase of the total sodium image can be explained by an increase of the unshifted compartments, i.e. either intracellular or, where the BBB is intact, extravascular sodium.

The MCAo leads to reduced perfusion in the infarcted regions and therefore the delivered amount of TmDOTP^{5-} is likely much smaller than in the untreated rat. Furthermore, TmDOTP^{5-} remains intravascular in healthy brain tissue which makes a proper estimation of the intracellular sodium in stroke by comparison with healthy tissue difficult. Thus, a transient MCAo in combination with an additional technique to open the BBB in the whole brain may allow for an estimation of the intracellular sodium signal increase after MCAo.

References

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