

Gd-DTPA Relaxivity in Rat Nervous Tissue

T. M. Shepherd¹, S. J. Blackband¹, G. J. Stanisz²

¹Department of Neuroscience, University of Florida, Gainesville, FL, United States, ²Imaging Research, Sunnybrook/University of Toronto, North York, Ontario, Canada

INTRODUCTION

Gadolinium contrast is frequently used for the clinical diagnosis of brain tumors and other mass lesions that disrupt the blood-brain barrier. Further, recent investigations have used the extracellular water relaxation properties of gadolinium chelates to estimate transmembrane exchange rates [1] and the intracellular fractions of nervous tissue [2]. Several previous reports have suggested that the relaxivity of gadolinium can vary with tissue environment [3,4]. To empirically determine gadolinium relaxivity in nervous tissue, we measured T_1 and T_2 rates in viable cortical brain slices superfused with different concentrations of Gd-DTPA-BPA (Omniscan). Unlike *in vivo* subjects, cortical slices provide a model of nervous tissue without an intact blood brain barrier or physiological mechanisms for gadolinium removal. Further, brain slices are sufficiently thin to allow complete, uniform infiltration of gadolinium chelates into the extracellular space after a short period of time. Cortical slices also can be described using a two-pool diffusion model with exchange [5] that generates independent estimates of mean intracellular fraction and transmembrane water exchange rates that are necessary to accurately calculate Gd-DTPA-BPA relaxivity based on T_1 and T_2 measurements.

METHODS

Vibratome-cut slices of rat cortex (500- μm thick) were procured from male P30 Long-Evans rats, then imaged using a multislice perfusion chamber inside a 600 MHz spectrometer with a 10-mm birdcage coil as previously described [6]. T_1 , T_2 and diffusion measurements at 3 diffusion times (T_d) were collected before perfusion with artificial cerebrospinal fluid (ACSF)(pH 7.4, 300 mOsm/kg) containing Gd-DTPA-BPA. Slices then were perfused for 30 minutes with ACSF containing 1 mM Gd-DTPA-BPA. Preliminary experiments suggested that this time was sufficient to reach equilibrium at the new Gd-DTPA-BPA concentration. Perfusion then was stopped for 30 minutes while T_1 and T_2 measurements were collected. This cycle then was repeated for ACSF containing 2, 4 and 8 mM Gd-DTPA-BPA. Previous studies demonstrate that slices remain viable under this perfusion protocol [6].

MR images were of limited in-plane resolution (128 x 64 matrix, 1.5 cm FOV) to improve signal-to-noise while reducing the time required per measurement. Slice thickness was 300 μm and the axial MR slices were placed in the middle of the 500- μm thick cortical slices to avoid the regions cut during procurement since these regions may have disrupted extracellular space and exposed intracellular compartments. Water diffusion in cortical slices was measured with a pulsed-gradient spin-echo multislice sequence with 12 diffusion-weighted images using diffusion gradients aligned with the read gradient (0-940 mT/m) and T_d 's of 10, 20 and 35 ms. These experiments had a 1.5 s relaxation time while echo time was minimized (23.5, 33.5 and 48.5 ms respectively). T_1 and T_2 values were measured in slices with saturation recovery (TR = 150 ms – 2 s in 10 steps) and fast spin-echo sequences (TE = 10 ms, 30 echos) respectively. To analyze the experimental data, a two-pool diffusion model with exchange [5] was used. This model assumes restricted diffusion in the intracellular space (that is dependent on diffusion time) and extracellular water diffusion mediated by tortuosity. The model allows for water exchange between tissue compartments. The model estimates the apparent diffusion coefficient in the extracellular space, the average cell dimension, the mean intracellular residence time and the intracellular volume fraction.

RESULTS

Diffusion and relaxivity measurements were obtained in 7 cortical slices. The two-pool diffusion model determined the mean residence time of water inside cells was 47 ± 2 ms and the mean intracellular volume fraction was 0.49 ± 2 (interpretation of the two-pool diffusion model in cortical slices is described in a separate report). Fig 1A shows saturation recovery data for cortical slices with lines fitted to raw data to determine T_1 relaxation times for cortical slices in different concentrations of Gd-DTPA-BPA. Fig. 1B shows the impact of increasing gadolinium concentrations on echo attenuation in cortical slices (lines fitted to obtain T_2 fits). The T_1 relaxivity for gadolinium was $4.0 \pm 0.1 \text{ mM}^{-1}\text{s}^{-1}$ for ACSF and $2.2 \pm 0.2 \text{ mM}^{-1}\text{s}^{-1}$ for the extracellular water of cortical slices. The T_1 relaxivity of ACSF at room temperature in a 600 MHz magnet is comparable to previously published values [2]. The T_2 relaxivity for gadolinium was $6.2 \pm 0.1 \text{ mM}^{-1}\text{s}^{-1}$ for ACSF and $6.1 \pm 0.2 \text{ mM}^{-1}\text{s}^{-1}$ for the extracellular water of cortical slices.

CONCLUSION

Our results indicate a significant differences for Gd-DTPA-BPA T_1 relaxivity in nervous tissue compared to aqueous solutions. In contrast to the previous studies however, T_1 relaxivity was lower than that of aqueous solutions. It is thus important to determine the changes in relaxivity for gadolinium chelates in nervous tissue otherwise data interpretation may be confounded.

REFERENCES

1. Quirk et al MRM 50:493-499 (2003), 2. Buckley et al. MRM 42:603-607 (1999), 3. Donahue et al. MRM 32:66-76 (1994), 4. Stanisz & Henkelman MRM 44:665-667 (2000), 5. Li et al MRM 40:79-88 (1998), 6. Shepherd et al. MRM 48:565-569 (2002), 7. Study funded by NIH RO1 NS36992 and P41 RR16105, 8. Thanks to Dan Plant for technical assistance.

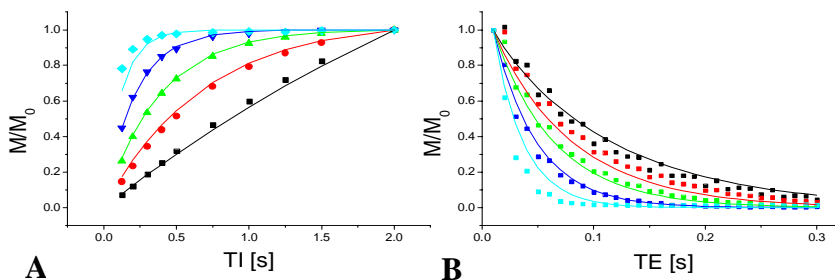


Figure 1 – saturation recovery and echo attenuation data from cortical slices in ACSF with 0, 1, 2, 4 and 8 mM Gd-DTPA-BPA.