Separating Intra- and Extracellular Water Signals in Rat Brain Using Gd-DPTA-Enhanced Diffusion-Weighted MRI

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Introduction

Diffusion-weighted MRI (DWI) is sensitive to acute ischemia in nervous tissue, yet the specificity of clinical DWI as a surrogate marker remains poor due to our limited understanding of the relationship between nervous tissue water diffusion and tissue microstructure. One key to this problem is to understand how intra-and extracellular (EC) compartmentation of water impacts the MRI signal obtained. Contrast-agent-enhanced NMR can be used to distinguish between the two compartments based on T_1 or T_2 differences [1, 2] and was recently applied to *in vivo* rat brain following intrathecal injection of Gd chelates [3,4]. Alternatively, the compartmental diffusion properties of tissue water can be calculated using an analytical model that incorporates intracellular (IC) restriction, EC tortuosity, and exchange rate between compartments [5,6]. Unfortunately, results from these alternative methods differ significantly, especially for the mean intracellular residence time of water (~ 505 ms and 75 ± 26 ms respectively). To investigate this disparity, we extended the contrast-enhanced approach [1, 4] to image rat-cortical slices perfused with different Gd-DTPA concentrations.

Methods

Cortical slices (500-µm thick) from male, P30 Long-Evans rats were imaged at 600 MHz using a multislice perfusion chamber [7] with a 10-mm birdcage coil (at room temperature). The slices were perfused with artificial cerebrospinal fluid (ACSF) containing 4 or 8 mM Gd-DTPA (Omniscan®). Equilibration of Gd-DTPA into the extracellular space of the slices was monitored hourly using inversion-recovery (IR) MRI measurements of tissue water T_1 (TI = 150 ms – 10 s) until a constant tissue relaxivity was observed. Then, a DW-IR spin-echo [1] MRI sequence with an adiabatic inversion pulse was used to collect MRI data at 16 inversion times (TI) and 5 (4 mM) or 7 (8 mM) *b* values. The TR was 1.5 s and 1.0 s for 4 and 8 mM Gd-DPTA, respectively (TE = 12.3 ms, FOV = 1.5 x 1.5 mm; 64 x 64 matrix; slice thickness = 0.3 mm; δ = 5.5 ms; Δ = 1.5 ms).

Results

Gd-DTPA relaxivity increased significantly from 1 to 3 hrs of equilibration [Fig. 1], suggesting that equilibration was not complete after 1 hour. Fig. 2 shows a plot of $\ln[(M_0\text{-}M_z(TR))/M_0]$ versus TI for slices equilibrated with 4 and 8 mM Gd-DTPA as a function of *b* value (only 8 of the 16 TI values are shown). If the [Gd-DTPA] is sufficiently high for the T_1 relaxation rate to be significantly faster than the rate of water exchange between the IC and EC compartments, then a plot of $\ln[(M_0\text{-}M_z(TR))/M_0]$ versus TI would be expected to be non-linear (i.e., non-monoexponential T_1 relaxation). Although the 4 mM data is linear, the 8 mM data is clearly non-linear, implying that the system is approaching the intermediate/slow exchange regime. However, the 8 mM data was not sufficiently bi-exponential to be fitted reliably, suggesting that this EC [Gd-DTPA] is still not high enough to dominate the effects of exchange between the IC and EC compartments.

Discussion

Intrathecal administration limits the maximum [Gd-DTPA] that is achievable in animal models (~5 mM) because excessive doses can induce seizures. Furthermore, it is difficult to maintain a constant, uniform distribution of contrast agent over time in the *in vivo* brain. The perfused brain-slice model, on the other hand, provides a uniform distribution of Gd-DTPA at a constant, known concentration following 2-3 hrs of equilibration (as seen in Fig. 1), significantly increasing the maximum achievable [Gd-DTPA] as well as the experimental time window relative to the *in vivo* model. These preliminary results suggest that the [Gd-DTPA] needed to achieve the intermediate/slow exchange regime in the brain-slice model exceeds 8 mM. This is in contrast to the results by Quirk *et al.* (4), who reported achieving the intermediate exchange regime (with biexponential T_1 recovery) using [Gd-DTPA] that are estimated to be less than 5 mM. Although it was not possible to estimate the mean intracellular water residence time from the current study, it appears to be significantly shorter in the brain-slice model than for the *in vivo* situation (since the onset of the intermediate/slow exchange regime is at a [Gd-DTPA] well above that likely achievable in animal models). This may support the short residence times predicted for rat cortical slices using the analytical model previously described [5,6]. Further DW-IR studies at higher [Gd-DTPA] (e.g. 16 mM) may better characterize these differences.

References and Acknowledgements

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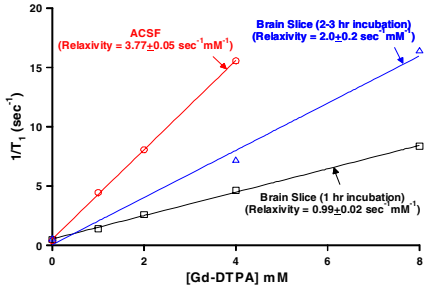

Figure 1 (left) – Effective relaxivity of Gd-DTPA in ACSF and brain slices as a function of time.

Figure 2 (right) – DWIR of brain slices in 4 and 8 mM Gd-DTPA as a function of *b* value.