Analysis of water diffusion in white matter using a hydration layer model

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Introduction

Diffusion measurements have been made with MRI for many years but an explanation for the observed behavior, in terms of the underlying mechanisms is still illusive. Diffusion decays have frequently been interpreted in terms of a two compartment model with the fast and slow diffusion coefficients associated with extra- and intracellular water, respectively. Unfortunately, the observed signal fractions are not consistent with the true ratio of intra- to extracellular water. Recently, LeBihan[1] has suggested that the two observed components may be associated with free water and hydration water rather than with intra- and extracellular water. It is reasonable to expect that intra- and extracellular hydration water will diffuse more slowly than the rest of the tissue water. The purpose of the research reported here was to investigate this suggestion to see if the predictions of this model are consistent with measured diffusion decay data.

In the past, many scientists have incorrectly considered the properties of cellular water to be very similar to bulk water. The special properties of cellular water are consequences of its polarization charge[2]. Hydrogen bonding of the water molecules with ligands on large proteins, which are abundant at cellular membrane surfaces, disrupts the normal pentagonal arrangements of nearby water molecules causing them to orient themselves in a cooperative manner radially to these charged groups[3]. Water molecules oriented in this fashion form what is known as a hydration layer around the proteins. In turn, the oriented charged water molecules in the primary hydration layer serve to orient adjacent water molecules to form a second hydration layer; and the water in the second hydration layer orients water molecules to form a third hydration layer; and so on. It has been shown that this multi-layered structure of hydration water is necessary for the proper biological activity of proteins[4].

Methods

All measurements were performed on a 1.5 T whole body clinical scanner (Siemens Symphony Quantum). One healthy volunteer was scanned 9 times. The protocol included DTI measurements and diffusion weighted imaging. For both, the matrix size was 128x128 and the field of view was 30x30 cm^2. DTI images were acquired in 12 gradient directions using b=0 and 500 s/mm^2 and TR/TE=4300/117 ms. Diffusion-weighted images were acquired for 96 b-values between 0 and 10 000 s/mm^2 with TR/TE=930/200 ms, Δ=50 ms and NEX=6. The diffusion gradients were rotated in the x-z plane in 15^o increments (α is the angle between the x-axis and the diffusion gradient direction). The 5 mm thick oblique-axial slice of interest included both the genu (GCC) and the splenium (SCC) of the corpus callosum (CC), as identified from a true mid-sagittal view. DTI Studio software[5] was used to compute and visualize the compact highly oriented fiber bundles of the CC. Signal values for the diffusion decays were taken as the mean over 9-pixel ROIs located in the GCC and the SCC, two regions with very high fractional anisotropy (FA). A new noise bias post-processing correction scheme was used to remove Rician bias[6]. Decay curves were fitted to a biexponential model using a Levenberg-Marquardt non-linear least-squares routine provided by Origin (Microcal Software Inc).

Results

The observed diffusion decays change considerably for α=30-90° and more subtly for α<30°. All decay curves agreed well with the assumed bi-exponential function. For α=0°, f_{slow}≈5% for both the SCC and the GCC, but increases with α. For α=90° the two components contribute about equally for both ROIs, although f_{fast} and ADC_{fast} are somewhat higher for the GCC than they are for the SCC. The observed FA values are the same for both ROIs.

α	ROI	FA	f_{fast}	ADC_{fast}	f_{slow}	ADC_{slow}
0	SCC	0.80 ± 0.04	0.95 ± 0.01	1.81 ± 0.08	0.04 ± 0.01	0.07 ± 0.03
0	GCC	0.80 ± 0.03	0.95 ± 0.03	1.74 ± 0.10	0.05 ± 0.03	0.09 ± 0.06
15	SCC	0.79 ± 0.03	0.95 ± 0.02	1.69 ± 0.06	0.05 ± 0.02	0.12 ± 0.03
30	SCC	0.79 ± 0.01	0.92 ± 0.03	1.50 ± 0.06	0.07 ± 0.02	0.13 ± 0.05
45	SCC	0.80 ± 0.02	0.87 ± 0.02	1.10 ± 0.08	0.12 ± 0.03	0.12 ± 0.04
60	SCC	0.79 ± 0.03	0.74 ± 0.04	0.82 ± 0.05	0.25 ± 0.03	0.11 ± 0.01
75	SCC	0.79 ± 0.02	0.52 ± 0.08	0.70 ± 0.06	0.46 ± 0.07	0.08 ± 0.01
90	SCC	0.80 ± 0.02	0.42 ± 0.06	0.66 ± 0.13	0.56 ± 0.06	0.06 ± 0.02
90	GCC	0.79 ± 0.03	0.60 ± 0.05	0.91 ± 0.21	0.35 ± 0.07	0.06 ± 0.02

Table 1. Fast and slow diffusion coefficients, reported as average ± stdev (x10^{-3} mm^2/s), and signal fractions, reported as mean ± stdev, for α = 0-90°, for the GCC and the SCC.

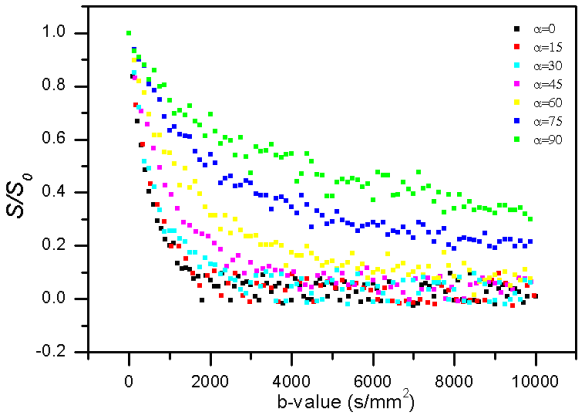

Figure 1. Experimental diffusion decay curves measured in the SCC with diffusion gradient angles α = 0-90°.

Discussion

Evaluation of water diffusion in the CC revealed two diffusion components for both the GCC and the SCC. If ADC_{slow} is assigned to the water in the inner hydration shells, as has been proposed by LeBihan[1], then the results for α=0 suggest that 4-5% of the signal is from this hydration water, whereas the α=90° results show that this contribution is 35-60%. This apparent contradiction can be explained if the water in the outer hydration shells diffuses more freely parallel to the axons than perpendicular to them. In this case, the outer hydration layers behave as "free" water for α=0° and contribute to f_{fast} and they behave as "bound" water for α=90° and contribute to f_{slow}. This is consistent with NMR measurements that have shown that hydration water diffusion is anisotropic[7]. The mobility of hydration water appears to be severely restricted especially perpendicular on the membranes. The membrane *and associated hydration layers* appear to form a barrier to water diffusion perpendicular to the membrane. This is also consistent with our observation that ADC_{slow} changes very little with α. Measurements for α=0 provide good estimates of cell water mobility assuming that most of the water (f_{fast} ≈ 95%) diffuses parallel to the membrane surface with ADC_{fast}. The value of ADC_{fast} depends on protein concentration since obstructions and water-protein interactions increase with macromolecular crowding[8] and membrane hindrance effects. If the hydration water is associated primarily with membrane bound proteins then similar behavior can be expected for intra- and extracellular water. Our results are also consistent with the observed high FA values since diffusion is higher for α=0 in the hydration layers and in the free water.

An important assumption inherent to this model is that the hydration water and the non-hydration water are not in fast exchange since, if they were, a single exponential decay would be observed. If cellular water molecules are considered to move like they do in free water, then hydration and non-hydration water would be completely mixed within 50 ms. However, there is considerable evidence to suggest that cellular water behaves more like a gel than a liquid. Our results confirm the anisotropy of hydration water diffusion and are consistent with the gel model of cellular water.

The results reported here for the GCC and the SCC are remarkably similar. The most significant difference is in the signal fractions for α=90°. However, the smaller hydration water fraction for the GCC correlates with reduced membrane surface area, consistent with smaller diameter fibers, on average, in the GCC[9].

References

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