ESTIMATION OF CELL MEMBRANE PERMEABILITY AND INTRACELLULAR DIFFUSION COEFFICIENT OF THE GRAY MATTER IN THE NORMAL HUMAN BRAIN

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Introduction

Diffusive transport of water in the presence of permeable membranes has a fundamental importance in biological tissues. Diffusion-weighted imaging (DWI) using magnetic resonance imaging (MRI) reflects the influence of the intra- and extracellular diffusion coefficient of water and cell membrane permeability. Previous diffusion MRI studies have focused mainly on measurement of the effective diffusion coefficient of water molecules in biological tissues, but details of the underlying microscopic structures were not clear. If we can formulate this relation or numerically predict the signals of diffusion MRI for samples having various microscopic structures, we can estimate the unknown diffusion parameters, such as the shape of the cells and membrane permeability. Our group proposed a method for estimating the unknown permeability of cell membranes based on a comparison of theoretically numerical simulations and experimental results using finite-difference method in our previous papers. Furthermore, we also evaluated the membrane permeability of leukocytes[1] and the rat brain[2] using a 4.7 T MRI system. The purpose of this study is to apply the proposed method to the normal human brain (gray matter) and to estimate its membrane permeability using a 1.5 T MRI system. One of our goals is to apply the proposed method to the diagnosis of brain disease. The estimated value of membrane permeability provides a reference for such diagnosis.

Materials and Methods

The study was approved by the Ethics Review Committee at the University of Tokyo Hospital and informed consent was obtained from each volunteer. All normal volunteers (three men, 19-21 years of age) underwent imaging with a 1.5 T Signa HDx MRI system (General Electric, Milwaukee, USA) equipped with a brain coil. MRI images were acquired from the volunteers using an echo planar imaging (EPI) sequence with applications of motion-probing gradient (MPG) pulses in three directions. The experimental signals were obtained from a cubic region (4.8×4.8×5 mm^3) in the gray matter of the precentral gyrus. We performed the diffusion simulation derived from the Bloch-Torrey equation using the finite-difference method. The DWI signals of biological tissues, which originate from the magnetization of water molecules, are acquired in synchronization with the application of MPG. The dynamics of the magnetization vector are expressed by the Bloch-Torrey equation consisting of Fick's second law of diffusion and the motion of the magnetization vector caused by MPG (Larmor precession). Simulations were performed on a numerical model of biological cells whose volume fraction of intracellular and extracellular spaces was 78:22. Each cell was modeled as an 18×18 μm^2 square, and was arrayed in 8 rows and 8 columns. The extracellular diffusion coefficient, D_{ext}, was 1.4×10^{-3} mm^2/sec. The MPG pulses were applied in the x direction with a pulse duration of δ=25 ms, pulse interval of Δ=50 ms, and intensity of up to G = 51.8 mT/m. The separations between the grid points and time steps were Δx = 0.5 μm and Δt = 40 μs, respectively. The cell permeability, P, and intracellular diffusion coefficient, D_{int}, of the gray matter were unknown parameters. Simulations were periodically performed for various combinations of these parameters. We defined the evaluative function as the difference between the signals of a numerical simulation and the experimentally obtained signals averaged over the three MPG directions. The above unknown parameters were estimated by finding a combination of parameter values using the following function:

$$F = \sum_i \left(S_{sim}(b_i, P, D_{int}) - S_{exp}(b_i)\right)^2 \qquad (1),$$

where $S_{sim}(b_i, P, D_{int})$ and $S_{exp}(b_i)$ are the signal intensities obtained from the simulation and the experiment, respectively. The combination of P and D_{int}, corresponding to the minimum value of F, gives the membrane permeability and the intracellular diffusion coefficient of the human brain.

Results and Discussion

Figure 1 shows the experimentally obtained signal attenuation in the gray matter of the precentral gyrus of the three volunteers shown in the upper right-hand image (b factor=4000 sec/mm^2). The logarithm of the signal intensities decrease with an increase in the b factor. The experimental results of this study indicate that when using b factors up to 4000 sec/mm^2, the signal attenuation in the gray matter of humans has nonlinearity because the diffusion of water in biological tissues is restricted by membranes and other microscopic structures. Figures 2 shows the relationships between the b factor and the logarithm of the signal intensity of the simulation for membrane permeability varied between 0.0 and 1.0×10^5 m/sec. The intracellular diffusion coefficient was equal to the extracellular diffusion coefficient ($D_{int} = D_{ext} = 1.4\times10^{-3}$ mm^2/sec). An increase in the membrane permeability caused a decrease in the signal intensity. The curves of P=0, 10, 100 μm/sec indicated nonlinear attenuation in particular. These nonlinear attenuation curves were derived from the restriction of diffusion by the membrane. Figure 3 shows the experimentally obtained signal attenuation of one volunteer. The combination of permeability, P, and intracellular diffusion coefficient, D_{int}, giving a minimum value of F, existed in each experiment. The figure also shows the result of the simulation for the estimated combination of P and D_{int}. The estimated intracellular diffusion coefficient and membrane permeability of the human brain were (1.0±0.0) $\times10^{-3}$ mm^2/sec and 76±9 μm/sec, respectively. Membrane permeability depends on the surrounding temperatures. In addition, the membrane permeabilities of biological cells depend on the measurement methods and the type of cell, ranging approximately from 1 μm/sec to 100 μm/sec. The permeability value estimated in this study was not far from the values obtained in previous studies. The samples used in previous studies for permeability measurement may be different from intact biological cells because those previous studies were carried out in vitro, and depended on the preparation of the samples and the environment of the measurements. This study is free of problems with the preparation of samples because we can non-invasively measure the diffusion MRI signals of living biological cells. The estimated values were the mean values of cells in a cubic region because the obtained signals were those of the region of interest. We could make a map of membrane permeability and intracellular diffusion coefficient distribution because the proposed method is theoretically applicable to any biological tissue. However, we estimated the membrane permeability and intracellular diffusion coefficient without considering the anisotropy of tissues in this study.

We estimated the membrane permeability and intracellular diffusion coefficient of the gray matter in the normal human brain. The method has the advantage of estimating the diffusion parameters of human cells in vivo using MRI. The permeability of the cell membrane depends on the species, state and environment of the cells and possibly reflects ischemia, infarction and edema. The estimated value of membrane permeability in this study provides a reference for the diagnosis of brain diseases in gray matter.

References

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[2]Imae T, Shinohara H, Sekino M, Ueno S, Ohsaki H, Mima K, Ootomo K. J Appl Phys 2008; 103, 07A311-1-3

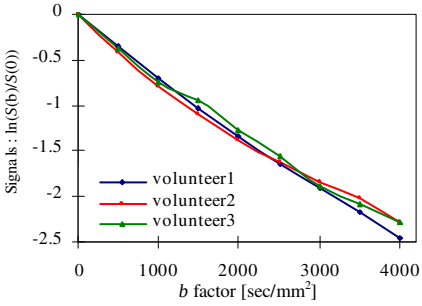

Fig.1 The experimentally obtained signals in gray matter of three volunteers.

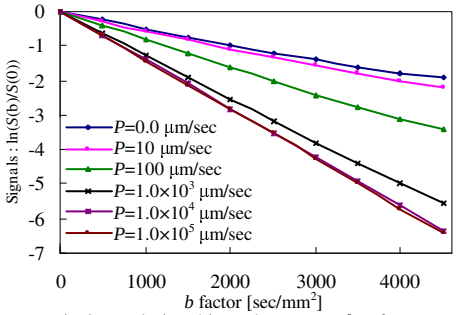

Fig.2 Relationships between b factor and logarithm of signal intensity of simulation for several membrane permeabilities.

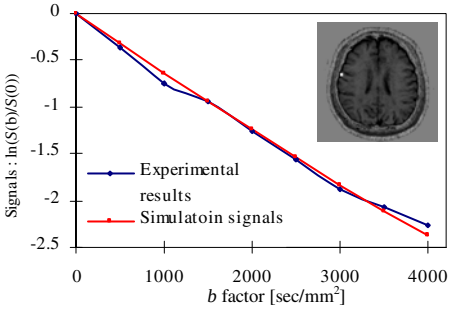

Fig.3 Experimentally obtained signal attenuation for one animal and numerical results corresponding to a minimum value of F.