Brain Capillary Water Permeability from Proton Density ^1H_2O Imaging in the Rat During Deuterated Saline Bolus Passage

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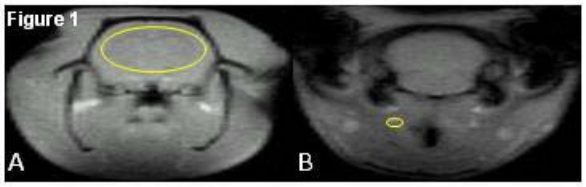
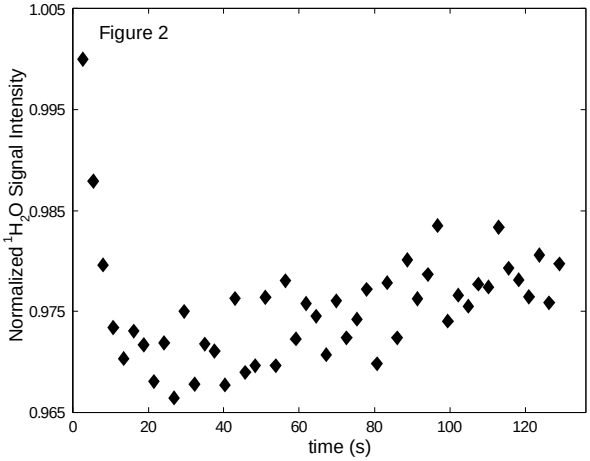
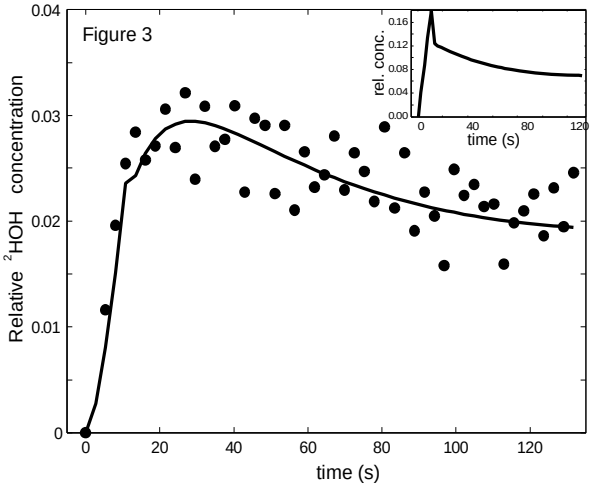
Introduction: *In vivo* intercompartmental water exchange has been studied extensively using labeled, including radiolabeled $^{15}OH_2$, water (1, 2). Here we use proton imaging to monitor the ^{2}HOH concentration change during a bolus injection of deuterated saline solution, and thence measure non-equilibrium transendothelial water transport. This provides a direct comparison of MRI results with those of $^{15}OH_2$ (scintillation detection) as well as offering valuable information about water transport in the brain, with a direct MRI measurement.

Methods: All experiments were conducted with an instrument featuring an 11.74 T, 31 cm inner diameter (ID) horizontal clear bore magnet (Magnex Scientific/Bruker Instrument) with a 9 cm ID gradient coil set insert. Each of five 450-500 g male Sprague-Dawley rats was anesthetized (isoflurane) and secured with its head inside a 3.8 cm ID Alderman-Grant RF transceiver volume coil. Each animal was monitored and maintained at physiological temperature, 37 (± 1)°C, throughout its experiment. A bolus of 2 mL (99%) ^2H_2O containing 0.9 w% dissolved NaCl was injected *via* the tail vein 0.5 - 2 min after acquisition initiation, and at a rate of 12 mL/min. A serial image series was obtained with an intersampling interval of 2.68 s. The FLASH sequence parameters were [TR = 42 ms, TE = 1.61 ms, FA = 10°, Matrix 256 x 64, FOV = 3.50 x 3.59 (cm)^2]. Two 3 mm coronal-equivalent image slices, 12 mm apart, were produced, one positioned in the brain and one in the neck.



Results: Pure ^2H_2O injected into a vein will redistribute to ^{2}HOH prior to reaching the carotids and brain. Figure 2 shows the brain ROI (Figure 1A) ^{1}H signal time course with baseline averaged to a single point. The ^{1}H signal intensity was transiently reduced due to the ^{2}HOH extravasation with consequent proton dilution. The ^{1}H signal decrease was used to estimate brain ^{2}HOH concentration. Each arterial input function (AIF) was obtained from bilateral ROI's (10-19 total pixels) within the two carotid arteries (Figure 1B, only the left artery indicated). The AIF time-course data were then fitted with a linear function for the uptake phase and a biexponential function for the washout phase (Figure 3 inset). A two compartment pharmacokinetic model adopted by Brix (3) was applied to the brain ROI ^{2}HOH concentration time-course. This ordinary differential equation system was solved step-by-step with different parameter sets using the Runge-Kutta method. In conjunction, a multi-dimensional grid search was used to find the parameter set giving the global chi square ($\chi^2 = \Sigma[S_{data} - S_{model}]^2$) minimum. The ^{2}HOH permeability surface area product (P_WS) is the only well defined parameter: P_WS mean (± SD) = 112.8 (± 29.8) mL/100g/min. This finding is in good agreement with values reported in a radiotracer $^{15}OH_2$ bolus study (1). Figure 3 shows the T_1 adjusted relative ^{2}HOH concentration time course (filled circles) with fitted curve from the search approach.





Discussion: Since blood flow velocity is sufficient to replenish the carotid artery section sampled within the 2D imaging slice, our AIF measurement is insensitive to ^1H_2O T_1 which likely varies during the bolus passage. In contrast, T_2 and T_2* are expected to be time-invariant since the bulk magnetic susceptibility of ^{2}HOH is essentially identical to ^1H_2O. Thus, proton density weighting of arterial [^1H_2O] signal is effectively maintained throughout the bolus time-series allowing for simple AIF estimation. A time-invariant T_1 relaxation weighting was not the case for brain parenchyma ^{1}H signal since deuterated water acts as a relaxation agent with a negative relaxivity (5) due to the deuteron's smaller dipole moment relative to that of the proton. Nevertheless, this is a small effect and readily corrected. For the brain, our calculations show the peak signal change due to difference in T_1, from ^{2}HOH bolus, is about 15% when maximum signal occurs. This has been corrected in the Figure 3 data. From these measurements we can estimate the average water molecule lifetime within a brain capillary to be ~ 0.6 s (= v_b/P_WS), somewhat longer than values obtained from equilibrium ^1H_2O exchange MRI measurement in the presence of intravascular paramagnetic contrast reagent (4). With further optimization it is expected that this approach will provide valuable information of normal physiology and pathology non-invasively and with relative ease.

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Reference: **1.** Go, Lammertsma, Paans, Vaalburg, Woldring, *Arch. Neurol.* **38**: 581-584 (1981). **2.** Ackerman, Ewy , Becker, Shalwitz, *Proc. Natl. Acad. Sci.*, **84**: 4099-4102 (1987). **3.** Brix, Bahner, Hoffmann, Horvath, Schreiber, *Radiology*, **210**: 269-276 (1999). **4.** Rooney, Li, Telang, Taylor, Coyle, Springer, *PISMRM*, **11**, 1390 (2004). **5**. Lee, Medina, Li, Telang, Micca, Coderre, Springer, *PISMRM* **9**:529 (2001).