Gd-Albumin Relaxivity in the Rat Thalamus *In Vivo* at 11.1 T

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Introduction

The relaxivity of an MR contrast agent (CA) parameterizes how efficiently a CA alters neighboring water proton longitudinal (T_1) and transverse (T_2) relaxation times. *A priori* knowledge of a CA relaxivity can be used in conjunction with pre- and post-contrast T_1-weighted scans and native T_1 values to determine the concentration of CA in a sample. CA relaxivity in solution can be readily determined by measuring the T_1 and T_2 dependence on CA concentration[1]; however, the relaxivity of the CA in solution may differ from that in tissue due to compartmentalization of water, binding of the CA to macromolecules, and changes in the microenvironment of the CA (e.g. - pH, temperature, microviscosity)[1-3]. Convection enhanced delivery (CED) is the direct infusion of an agent into the extracellular space of tissues via a positive pressure gradient and has emerged as a promising local drug delivery method for treating neurological diseases. As a surrogate for therapeutic agents, the macromolecular CA, gadolinium-labeled albumin (Gd-albumin), has been infused into the rat dorsal and ventral hippocampus to determine the influence of tissue architecture on infusate distribution[4]; however since the relaxivity of Gd-albumin in tissue is unknown, only the final distribution volume of the CA could be compared between ventral and dorsal distributions following CED. Measuring the relaxivity of Gd-albumin in the rat brain, *in vivo,* would enable the direct measure of CA concentration profiles, rather than just the spatial distribution, which are more closely related to therapeutic efficacy in a targeted region. In this study, the relaxivity of Gd-albumin was measured in the rat brain thalamus *in vivo* at 11.1 T. These tissue relaxivity values were compared to relaxivity values in solution to assess the error associated with applying solution-based relaxivity values to *in vivo* tissue CA concentration calculations. The measured CA relaxivity in tissue can be used to directly determine CA concentration in similar brain regions.

Methods

Experiments were performed on 250-275 g Spraque-Dawley rats (n = 6) using approved protocols and procedures. In addition to a control solution of artificial cerebral spinal fluid (aCSF), a stock of Gd-albumin (MW ~87 kDa, ~35 Gd-DTPA molecules per albumin; R. Brasch Laboratory, University of California, San Francisco, CA) was diluted in aCSF and tagged with Evans blue dye to produce CA infusion solutions with concentrations of 0.033, 0.024, and 0.016 mM. For the infusion of the four solutions, a silica cannula was stereotaxically placed in a different region of the rat thalamus and 2.2 µl of infusate was delivered at a rate of 18 µl/hr. Following the infusion surgery, the rat was placed in a custom, MR-compatible, stereotaxic frame designed to fit inside of a transmit-only, quadrature birdcage volume coil. A receive-only, quadrature surface coil was then placed on the head of the rat (Fig 1). T_1 and T_2 measurements were acquired with a spin echo sequence using axially-oriented slices with a 2.4 × 2.4 cm FOV, matrix size of 104 ×104 with 10, 1 mm thick slices and 2 averages. Spin echo T_1 progressive saturation data was acquired with TR = 5000, 2000, 1500, 1000, 750, 500 and 250 ms and TE = 15 ms. T_2 data was acquired with a minimally diffusion-weighted spin echo sequence with TE = 15, 20, 25, 30, 45, 60 and 75 ms and TR = 2000 ms. Regions of interest (ROI) were drawn to encompass the distributed CA at each infusion site (Fig 2) and T_1 and T_2 were calculated using a saturation-recovery model and spin-echo decay model, respectively. T_1 and T_2 data was imported into R^5 to determine R_1 and R_2 relaxivity by linear regression according to $1/T_i=1/T_{i0}+R_i[CA]$ with i=1,2. The tissue concentration of CA was calculated by assuming a porosity of 30% in the thalamus[6].

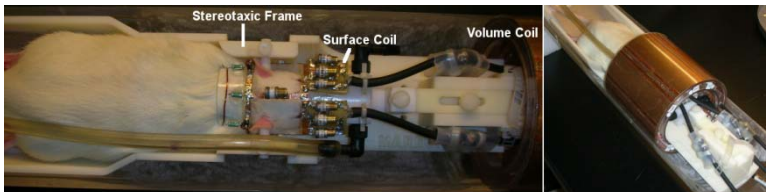

Figure 1 – (Left) View of rat in MR compatible stereotaxic frame with volume coil removed. (Right) Rat in stereotaxic frame with volume coil in position for MR imaging.

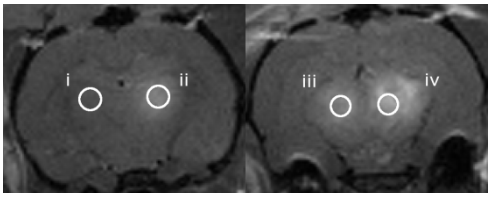

Figure 2 - Distribution of i) 0, ii) 0.016, iii) 0.024 and iv) 0.033 mM solutions of Gd-albumin in aCSF (circles indicate ROI).

Results

Measured T_1 and T_2 values varied less than 12% and 7%, respectively, within each infusion site group and decreased, as predicted by theory, with increasing concentration of CA. Linear regression revealed a R_1 relaxivity value of 22.2 $mM^{-1}s^{-1}$ ($r^2 = 0.93$) and R_2 relaxivity value of 355 $mM^{-1}s^{-1}$ ($r^2 = 0.85$) in the rat thalamus *in vivo* (Fig 3). In comparison, R_1 and R_2 were found to be 104 $mM^{-1}s^{-1}$ ($r^2 = 0.99$) and 520 $mM^{-1}s^{-1}$ ($r^2 = 0.98$), respectively, in solution.

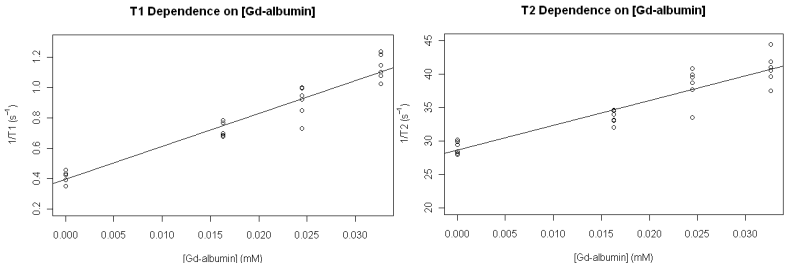

Figure 3 – Fit of linear model to T_1 (left) and T_2 (right) data in the rat thalamus for different concentrations of CA.

Conclusions

In this study, a custom built quadrature receive only coil and MR compatible stereotaxic frame were successfully employed to measure the R_1 and R_2 relaxivity of Gd-albumin delivered to the rat thalamus *in vivo* by CED at 11.1 T. *In vivo* relaxivity values demonstrate a 78% and 32% reduction in R_1 and R_2 relaxivity, respectively, in comparison to values measured in solution. Using relaxivity values measured in solution will introduce significant errors into the calculation of brain CA concentration.

References

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Acknowledgments

The project described was supported by award number R01NS063360 from the National Institute of Neurological Disorders and Stroke. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute Neurological Disorders and Stroke or the National Institutes of Health. The authors would also like to thank Barbara Beck for her help in constructing the quadrature surface coil.