Changes in Blood-Brain Barrier Permeability and Blood Volume During MS Lesion Development and Evolution

J. M. Njus[1], X. Li[1,2], C. S. Springer[1,2], M. Taylor[3], T. Greisel[1], F. W. Telang[2,4], P. K. Coyle[3], and W. D. Rooney[1,2]

[1]Advanced Imaging Research Center, Oregon Health and Science University, Portland, OR, United States, [2]Chemistry Department, Brookhaven National Laboratory, Upton, New York, United States, [3]Neurology Department, Stony Brook University, Stony Brook, New York, United States, [4]Medical Department, Brookhaven National Laboratory, Upton, New York, United States

Introduction

Disruption of the blood-brain barrier (BBB) is thought to be an early or initiating event in new multiple sclerosis (MS) lesion development.[1-5] Retrospective analysis revealed that before lesions become visually apparent in MR they exhibit very subtle gadolinium contrast reagent (CR) enhancement, relative to MS normal appearing white matter (NAWM).[3] Whether this indicates an increase in BBB permeability and/or blood volume prior to lesion development is unclear because a pharmacokinetic component was not included.[3] Findings of reduced magnetization transfer ratios (MTRs),[2,3] increased water content,[3] increased apparent diffusion coefficients (ADCs),[4,5] and abnormal cerebral perfusion[5] have been reported in pre-MS lesion NAWM. However, while CR BBB permeability in an MS lesion has been measured,[6] quantitative BBB permeability changes throughout the course of lesion development have not been examined. In this study, we use DCE-MRI to quantify the CR BBB permeability time-course during lesion development in relapsing-remitting MS (RRMS) brain tissue.

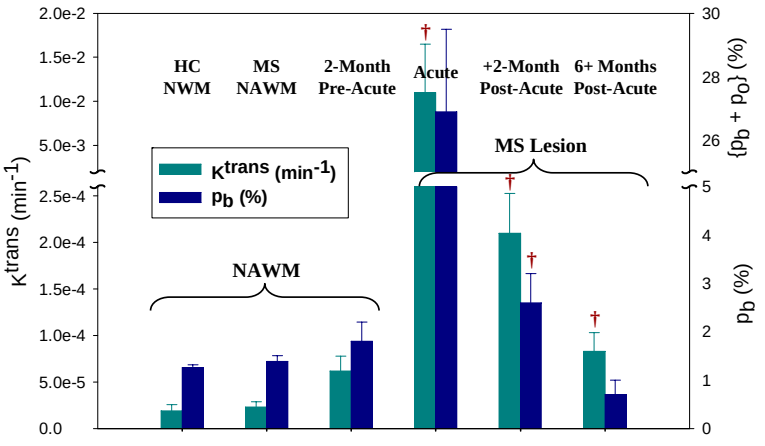
Methods

12 healthy controls (HC) [7 women, mean age 33 (± 12), and 5 men, mean age 33 (± 9) y] and 16 RRMS subjects [9 women, mean age 35 (± 7) and 7 men, mean age 40 (± 8) y] provided informed consent before participating in this study. All MR data were obtained using a 4 T Varian INOVA instrument. The experimental details pertaining to data collection and quantitative R_1 mapping are as reported elsewhere.[6-9] Data for ^1H_2O R_1 [$\equiv T_1^{-1}$] measurement were collected prior to, and at five times after, CR (Gadoteridol, Prohance; Bracco) injection.[6] Each RRMS subject was examined every two months over the course of about one year. CR BBB permeability was determined as K^{trans} (the volume transfer constant of CR across the BBB)[6] using a two-compartment (for CR and for water) model that accounts for equilibrium intercompartmental exchange of water molecules.[9-12] MATLAB 7.0 was used to obtain the K^{trans} and mole fraction blood (p_b) and/or interstitial (p_o) water values (i.e. related to the CR fractional distribution volumes)[9-12] *via* multi-parameter fittings of region-of-interest (ROI) data for NAWM and NAGM areas. The details pertaining to NAWM and NAGM ROI selection have been reported elsewhere.[8,9] Pre-lesion NAWM ROIs were determined retrospectively, from scans revealing the onset of visually enhancing, acute MS lesions (i.e. hyperintense relative to NAWM in post-CR R_1 maps). Likewise, 2-month post-acute lesions (i.e. hypointense relative to NAWM) ROIs were measured from scans taken after lesion onset. All of a subject's serial scans were co-registered using a rigid-body transformation technique. To avoid partial volume averaging only large (> ~100 μL) lesions were examined. Statistical analyses were performed using SPSS 15.0; MANCOVA was used to estimate the effects of disease on mean p_b and K^{trans} values; pre- and post-acute lesion ROIs were compared to the mean ROI values of NAWM areas that did not reveal any visible disease activity. Corrected P values < 0.05 were considered statistically significant.

Table 1. MS vs. HC group comparisons of mean K^{trans} and p_b values (±SE)*.

		HC (n = 12)	MS (n = 16)	% Diff. MS > HC
K^{trans} (min^{-1}):	NAWM	1.9×10^{-5} ($\pm6.8\times10^{-6}$)	2.3×10^{-5} ($\pm5.8\times10^{-6}$)	20%
	NAGM	2.2×10^{-5} ($\pm6.1\times10^{-6}$)	3.4×10^{-5} ($\pm8.5\times10^{-6}$)	52%
p_b:	NAWM	0.013 (±0.001)	0.014 (±0.001)	10%
	NAGM	0.023 (±0.001)	0.028 (±0.001)	24%†

Note: †Statistically significant (P < 0.05); *Standard Error (SE)



Results

Table 1 summarizes the results from comparisons of mean K^{trans} and p_b values between the HC and MS groups. MS-associated increases were observed in the mean K^{trans} and p_b values of both NAWM and NAGM. However, the only statistically significant change was an increase in the mean NAGM p_b value. The serial results are summarized in **Figure 1** (see caption for details), where the temporal progression from normal WM to chronic MS lesion runs from left to right. Compared with MS NAWM, the temporal trend was increased mean K^{trans} values for the 2-month pre-acute NAWM, acute, 2-month post-acute, and 6+ month post-acute phases of lesion evolution; all except the 2-month pre-acute lesion NAWM increase were statistically significant. Similar trends were observed in the mean p_b values, with the exception of a decrease in the 6+ month post-acute lesion value. The only statistically significant finding was an increased mean p_b value in the 2-month post-acute lesions.

Discussion

Our results suggest that fractional blood volume and a BBB permeability increase in normal appearing MS brain tissue. In the serial data, the trend of increased BBB permeability to CR in pre-lesion NAWM, peaking in the acute lesion, and followed by a steady decline in the post-acute phase (although not to baseline values), is consistent with *post-mortem* studies indicating widespread tight-junction abnormalities in chronic MS lesions.[13,14] A similar evolution is also observed in the pre- and post-acute lesion p_b, though it returns to a value *less* than baseline in the 6+ month post-acute lesion state; consistent with the findings of a longitudinal perfusion study; where CBV and CBF values dropped below baseline.[5] The results of this *in vivo* study clearly indicate extensive microvascular changes during MS lesion development and BBB permeability that remains elevated even in chronic MS lesions.

Figure 1. Mean p_b (right ordinate) and K^{trans} (left ordinate) values of HC normal white matter (NWM), MS NAWM, and at different phases of MS lesion development. The error bars represent ±SE of the group mean value. For the acute lesion values, the CR distribution volume represents the mole fraction of blood water, p_b, plus the mole fraction of interstitial water, p_o (i.e. the extracellular extravascular space); defined on the right vertical axis as $\{p_b + p_o\}$. †Statistically significant ($P < 0.05$) with respect to MS NAWM: statistical analyses performed by comparing the mean lesion (and pre-acute NAWM) p_b and K^{trans} ROI values to the mean NAWM ROI values of each particular subject (i.e. paired data).

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