Quantification of blood-brain barrier permeability in the mouse brain in vivo: a longitudinal study

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Introduction

The blood-brain barrier (BBB) plays a crucial role in protecting the brain from the entry of various neurotoxic or neuroactive agents. Impaired BBB function has been implicated in a variety of diseases including multiple sclerosis and traumatic brain injury for both pathogenesis and disease progression. Therefore, non-invasive in vivo measurement of BBB permeability is of importance in understanding the disease mechanisms and evaluating potential agents that modify BBB permeability. We have previously shown that quantitative measurement of BBB permeability in the mouse brain is feasible using the MRI based multiple time-graphic method (Patlak plot) following intravenous administration of contrast agent [1]. However, repeated measurements of the permeability is challenging due to the requirement of accessing arteries in mice for the contrast agent administration. In this study, we report a new approach that permits repeated measurements of BBB permeability by combining intraperitoneal (i.p.) contrast agent administration and quantitative T_1 mapping technique. By using the new approach, we have successfully measured BBB permeability changes over two weeks following a traumatic brain injury in mice.

Methods

Nine C57BL/6 mice (3 months old male) underwent surgery with a controlled cortical impact (CCI) described previously [2]. At days 3 (D3), 7 (D7) and 14 (D14) following CCI, MRI studies were performed to measure BBB permeability. MRI was performed at 9.4 T Varian system equipped with a 12 cm gradient insert (40 G/cm, 250 μs) (Varian Inc., CA). A 6-cm diameter Helmholtz volume transmit coil and a 7-mm diameter surface receive coil were used for MR imaging. Animals were handled following the Institutional Animal Care and Use and their physiological conditions were monitered during MR scans (core body temerature and respiration rate). T_2-weighted MR images were acquired using a multi-slice spin echo sequence (FOV = 2x2 cm^2, matrix = 192x192, TE/TR = 60/1500 ms, nt=2, thk = 0.5 mm) and T_1 mapping was performed using a modified Look-Locker multislice sequence to acquire multiple phase encodings per inversion pulse (TR/TE = 4/2 ms, FOV = 2x2 cm^2, matrix = 128x128, thk = 0.5 mm, flip angle = 20°, 22 inversion times, acquisition time = 8.5 min). To determine the optimal waiting time post Gd-DTPA MRI, two mice were scanned every hour up to 4h after Gd-DTPA (Magnevist, Berlex) administraion (0.2 mmol/kg). Remainder of 7 mice were scanned for T_2-weighed MRI and T_1 mapping before and 2h after Gd-DTPA administration. The BBB permeability index was estimated with $R_1 \equiv 1/T_1$ changes obtained from the three regions of interest in the brain as shown in Fig. 2(a).

Results and Discussion

Figure 1 shows the time course of R_1 changes in the normal appearing cortical area in ipsilateral side (CCI-peri, box 3 in Fig. 2 (a)) of two mice. Based on the time course of R_1, the waiting time was determined to 2h and applied to all other animals. Figure 2 shows a T_2-weighted image at D14 when the development of edema is evident and pre- and post-contrast T_1 maps at P3. Rectangles in Fig. 2(a) indicate ROIs in which T1 values were obtained (1: CCI-core; 2: contra-lateral cortex; 3: peri-injury region) The cortical areas with tissue damages by CCI are clearly visible as T^2 hyper-intensities in (a). Increased BBB permeability can be seen in the areas of CCI injury as indicated by shortening of T_1 in (c) compared with (b). Figure 3 shows longitudinal BBB permeability changes at D3, D7 and D14 in each ROI. Both the core of CCI and peri-CCI cortex showed large initial BBB opening and gradual closing over time. No BBB opening was observed in contralateral cortex. The pattern of BBB opening in CCI-core and CCI-peri at D3 was consistent with our previous report.

The current study demonstrates the feasibility of longitudinal BBB permeability measurement in the mouse brain in vivo by combing i.p. delivery of Gd-DTPA and T_1 mapping technique.

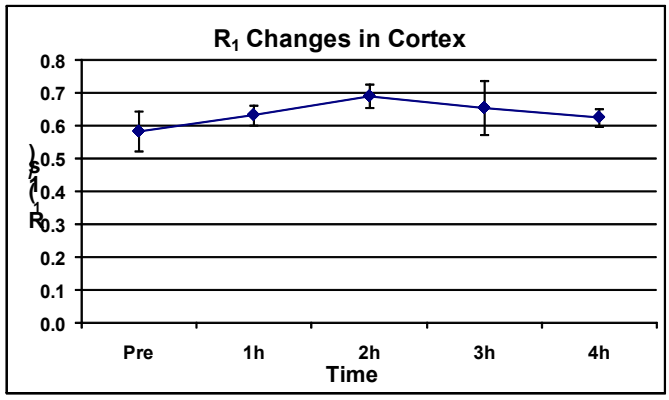

Fig. 1. R1 time course in cortical region (box 2 in Fig 2 (a))

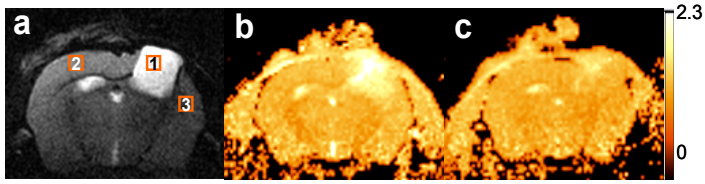

Fig. 2. (a) T2-weighted images at D14 and T_1 maps acquired (b) before and (c) after Gd-DTPA administration at D3. Orange rectangles indicate ROIs in which T_1 values were obtained.

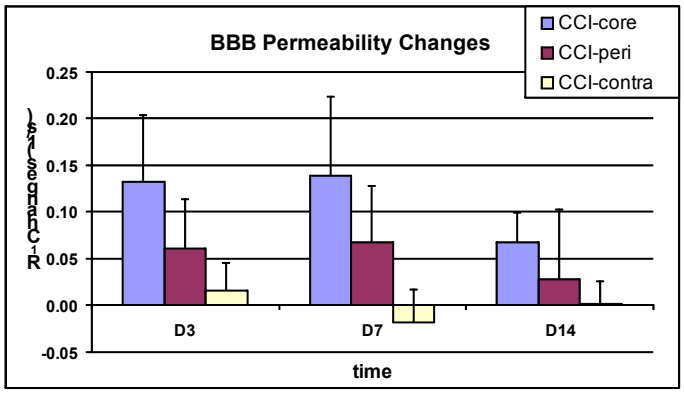

Fig. 3. Longitudinal changes of BBB permeability following CCI in three ROIs at D3, P7 and P14.

References

[1] Lee et al, ISMRM (2010) [2] Bilgen et al., *Neurorehabil Neural Repair* 19:219-26 (2005) [3] Onyschuk et al., J Neurotrauma 25:153-171
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