Dynamic Changes in Blood-Brain-Barrier permeability after transient focal cerebral ischemia in rats

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Synopsis

The association of CBF and CBV with angiogenesis after transient focal cerebral ischemia has been documented. However, the relationship between the changes in cerebral hemodynamics and disruption of blood-brain barrier (BBB) permeability, which is a possible mechanism causing reperfusion injury, is unknown. In the present study, dynamic contrast-enhanced MRI (DCE-MRI) was applied to investigate the temporal changes of BBB permeability, K^{trans}, in rats subjected to 60 mins of middle cerebral artery occlusion (MCAO).

Introduction

We have previously reported that the increase in both CBF and CBV is tightly coupled to the increase in vascular density, a sign of angiogenesis, in the ipsilateral cortex after 60 mins MCAO [1]. However, the exact mechanism or mechanisms and physiological significance of these changes remain obscure. The BBB is critical for brain homeostasis and is located at the cerebral endothelial cells. After stroke, there is a disruption of the BBB. The relationship between alterations of BBB permeability and post-ischemic angiogenesis is not clear. In recent years, dynamic contrast-enhanced MRI (DCE-MRI) has been widely employed to investigate the vascular properties of pathology tissues [2]. The purpose of the present study was thus to apply DCE-MRI to investigate the changes in BBB permeability, K^{trans},over time in relation to hemodynamics and angiogenesis in a well-defined three-vessel occlusion model in the rat.

Material and Methods

Six male Long-Evan rats (250~300g) were subjected to transient MCAO for 60 minutes. The rat, anesthetized with chloral hydrate (360 mg/kg body weight, i.p.), was placed in a prone position and fitted with a custom-designed head holder inside the magnet, as previously described [1]. All MRI experiments were performed using a 4.7 T Biospec 47/40 spectrometer with an active shielding gradient (5.6 G/cm in 500 μs). Images were acquired at day 1, day 2, day 3, day 5, day 7, day 10 and day 14 after 60 minutes of transient ischemia using a 20 cm volume coil as the transmitter coil and a separate 2 cm surface coil for signal detection. T2-weighted and DCE-MRI were scanned in the same location with a FOV of 4cm, a slice thickness of 2mm. T2-weighted MRI was acquired using RARE sequence with a TR of 3000ms, a TE of 80ms and a matrix size of 256*128. For DCE-MRI, a dynamic series of 25 spin-echo T1-weighted images were acquired with a TR of 400 ms, a TE of 10ms and a matrix size of 256*64. The bolus intravenous injection of 0.2 mmol/kg Gd-DTPA was performed on the sixth temporal frame.

Quantitative analysis of DCE-MRI data was based on four compartmental model of Tofts and Kermode [3]. ROIs were determined by manually tracing the cortex of both ipsilateral and contralateral hemispheres after optimizing the contrast. The [Gd] concentration- time curve was fitted by using Nonlinear Regression Analysis to obtain optimal k^{trans}. The k^{trans} was calculated and visualized using MATLAB (MathWorks, Natick, MA, USA) and MRVision (MRVision Co., Menlo Park, CA), respectively. The k^{trans} map was also performed on a pixel-by-pixel basis and co-registered with anatomical images. Paired Student's t-test was used to compare the k^{trans} and v_e at different time points. $P<0.05$ is considered to be significant.

Results

Fig. 1 shows a representative set of T2-weighted images and k^{trans} maps from a rat subjected to 60 min of transient MCA occlusion at different time points and from a sham-operated rat. The increase in k^{trans} was observed in the ipsilateral cortex, particularly in the outer cortical layers. A significant increase in k^{trans} was also observed in the contralateral cortex which is in agreement with a pervious report that subtle changes in capillary density are noted in the contralateral cortex in the MCAO model [4]. A quantitative analysis of the temporal changes in the k^{trans} in the ROI within the ipsilateral cortex is shown in Fig. 2. k^{trans} in the ipsilateral cortex gradually increased and peaked at day 7 after reperfusion at a level 5.3-fold higher than in the sham-operated controls, and then slightly decreased at day 10 and day 14, but were still significant higher than the controls ($p<0.05$). The trend of changes in k^{trans} after reperfusion is well correlated with the hemodynamic changes that are tightly coupled to the sign of angiogenesis.

Conclusion

The present results demonstrate that DCE-MRI is a useful method to evaluate the k^{trans} over time following ischemia and reperfusion, and the relationship between vascular density and permeability is closely related. The use of parameter of k^{trans} could provide new insights into the status of microvascular structure in a transient MCAO model in rat.

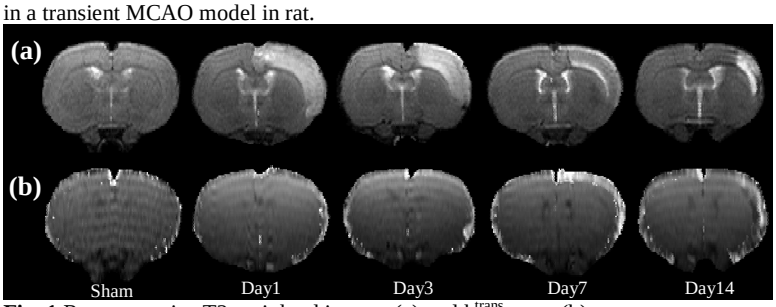

Fig. 1 Representative T2-weighted images (a) and k^{trans} maps (b) at the indicated time-points, respectively in a transient MCAO model of 60 mins duration, in rat.

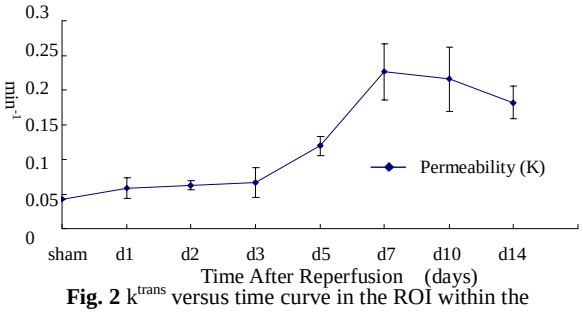

Fig. 2 k^{trans} versus time curve in the ROI within the ipsilateral cortex.

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