An Index of Blood-Brain Barrier Permeability Measured by Serial MRI in Experimental Stroke

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Introduction

This study sought to quantitatively characterise the time course of blood-brain barrier (BBB) permeability in a rodent model of ischemia in both the acute (1-24 hours post-occlusion) and chronic (7-14 days post-occlusion) phase. Disturbances in the BBB have been reported during the acute period [1], however the integrity of the BBB during the chronic phase is less well known. Due to the lack of success in developing acute neuroprotective therapies, a new generation of agents designed to promote functional recovery are being developed for ischemic stroke interventions. Typically, these are complex molecules that cannot cross the BBB, however, disturbances in the BBB identified in this study may indicate a therapeutic window, allowing delivery of agents into the affected region.

Methods

Male Sprague Dawley rats (pre-surgery weight 299±30g) were imaged at 7 time points (n = 6-15 per time point): 3 days before and 1, 6, 12, and 24 hours and 7 and 14 days after 90 minute transient middle cerebral artery occlusion (tMCAO) [2]. At each time point T_2 and T_1 weighted images (WI) pre- and post-administration of Gd-DTPA (*Magnevist* 0.65mmol/kg via intravenous catheter), were acquired using a 4.7 T Varian animal imaging system (spin echo, NEX = 4, T_2WI: TR/TE = 2000/70 ms, T_1WI: TR/TE = 1100/20 ms). Contiguous coronal slices of 1mm thickness were used to image the whole brain with an in-plane resolution of 0.5 x 0.5 mm. Lesion volumes, apparent on T_2WI were measured using a semi-automated method to confirm successful application of the experimental stroke technique. Since Gd-DTPA cannot normally cross the BBB, appearance in the brain parenchyma is used as a marker of BBB breakdown. An in-house application was used to calculate the percentage difference in signal intensity (SI) between the pre- and post-contrast T_1WI on a pixel-wise basis (Fig. 1). A BBB permeability index (BBBPI) was formulated by calculating the mean percentage difference in SI of all pixels within a region of interest (ROI). Regions investigated included an area representative of the whole lesion (Fig. 2), its cortical and subcortical components, the thalamus and the striatum. For each ROI the BBBPI was also calculated in the homologous area in the contralateral hemisphere for comparison.

Results

Lesion volumes were consistent with previous studies (at 24 hours 219±38mm^3, mean±SE) [2][3]. As expected, the mean BBBPI was the same (paired t-test) in both hemisphere ROIs pre-occlusion (Fig. 3a, first data point). Two-way repeated measures ANOVA matched by hemispheres and Bonferroni post-hoc tests were used to compare the BBBPI at each subsequent time point to the pre-occlusion BBBPI. The BBBPI in the ipsilateral ROI was slightly increased in the acute period at 6 hours but became statistically different at 7 days ($p<0.001$) and 14 days ($p<0.01$) (Fig. 3a). The temporal pattern of BBBPI appears similar in the cortical and subcortical sections of the lesion (dashed lines). Quite different patterns of parenchymal enhancement were seen comparing the striatum and the thalamus (Fig. 3b and 3c): the former is typically made ischemic by tMCAO (a mean BBBPI of 7.0 ± 1.8% at 7 days in the striatum was the greatest of all the ROIs assessed), while in the latter, lesions are not usually seen on T_2W images (the BBBPI measured in the thalamus at all time points was not statistically different to pre-occlusion values).

Conclusion

The data indicates that there is a significant increase in BBB permeability at chronic time periods, corroborating human results [4]. This late opening of the BBB may have practical clinical advantages for drug administration. Overall, the results suggest that the optimal time for drug delivery across the BBB, in this stroke model, is between 24 hours and 14 days for drugs targeting delayed processes.

References

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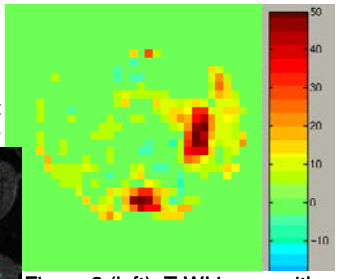

Figure 1 (right). Representative percentage difference image at 7 days post tMCAO

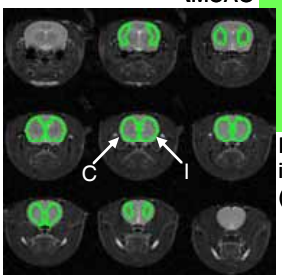

Figure 2 (left). T_2WI image with ipsilateral (I) and contralateral (C) ROI overlaid

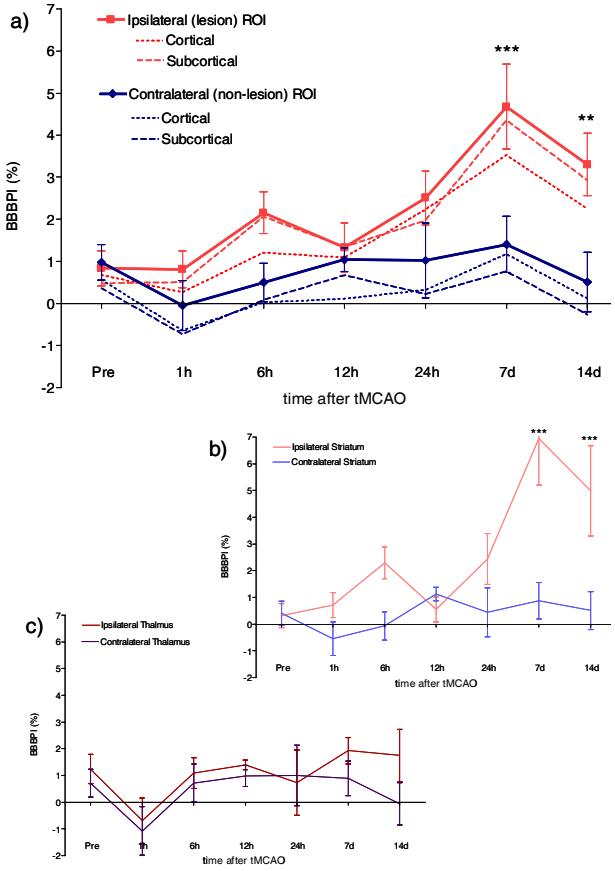

Figure 3. Temporal evolution of BBBPI in various ROI for both the ipsilateral and contralateral hemispheres. a) Lesion and cortical and subcortical components, b) Striatum c) Thalamus. Significant differences in BBBPI at time point compared to pre-lesion baseline BBBPI in ipsilateral hemisphere denoted (*** $p<0.001$, ** $p< 0.01$).