Quantitative evaluation of BBB blocking property of BB1101 using MRI

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Introduction

Disruption of the blood-brain barrier (BBB) occurs during the neuroinflammatory response to cerebral ischemia. Proteases are an important component of that response. Proteases of the serine and matrix metalloproteinase (MMP) gene families have been shown to degrade proteins of the basal lamina around blood vessels contributing to the proteolytic breakdown of the BBB. Because MMPs are upregulated in focal cerebral ischemia and play a role of paramount importance in BBB opening, the effects of BB1101, an inhibitor of MMP activity, on BBB permeability in rat models of ischemic stroke were investigated in this study. An MRI technique for estimating barrier permeability coefficient, k_i based on the graphical analysis method [1] has been used for testing newer pharmaceutical molecules. This technique involves quantifying temporal distribution of gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA) in the brain tissue and fitting the data to a tracer kinetic model. The main aims of the study were 1) To investigate the BBB blocking property of BB1101 at 3 hrs post MCAO in treated rats using MRI technique. 2) To obtain a quantitative estimate of stroke infarct size at 48 hr post MCAO in rats treated with BB1101. 3) To evaluate the effect of BB1101 on neurological recovery of rats.

Materials and Methods

Focal cerebral ischemia was induced in the rat by inserting a nylon filament through the external carotid artery in order to occlude the middle cerebral artery (MCA) for 2 h. Animals were studied at 3 h of reperfusion (a time point at which early BBB opening occurs in this model), and after 48 h of recirculation. The animals were divided into two groups - control and BB1101 treated rats. Treated rats received 30mg/kg of BB1101 injected intra-peritoneum prior to surgery (T=0), at T=24 hrs and T=48 hrs post MCAO. MR Imaging was performed on a dedicated research Bruker 4.7T MR scanner on each rat at 3 hrs and 48 hrs post MCAO to acquire T2-weighted, DWI images and quantitative T1 maps. After acquiring baseline images, 0.1 mM/Kg of Gd-DTPA was injected and a time series of inversion recovery MR images were acquired over 40 mins using a Look-Locker based MR technique. The following optimized MRI parameters were used: 2D IR-True-FISP, TR/TE 2.8/1.48ms, FOV 3.2 X 3.2 mm, slice thickness 2 mm. T1 map for each slice for each time point was constructed using a three parameter least square fit to pixel signal intensity values. Data were post processed pixel-wise to generate Gd-DTPA concentration and permeability coefficient color maps. Lesion size was estimated from ADC maps using thresholding techniques. The tissue was considered to be ischemic if the pixel ADC values in the ipsilateral hemisphere were 77% of the contralateral hemisphere.

Results & Discussion

Based on the Ki values obtained from permeability maps, results suggest that inhibition of MMP by BB1101 significantly reduced extravasation of Gd-DTPA and the area of leakage (Fig. 1). However, BB1101 failed to significantly reduce infarct volume as assessed (using ADC maps) see Fig. 2. In addition, treatment with this broad spectrum MMP inhibitor worsened the neurological recovery of rats, evaluated for 4 weeks following the ischemic event. The mechanism of this detrimental effect at later times is thought to involve inhibition of angiogenesis and neurogenesis, which require MMP action. These studies indicate that MMP inhibitors might be beneficial at early times after stroke in order to reduce BBB breakdown, which could extend the time window for thrombolytic therapy, but longer term use may bring out detrimental effects.

Reference. [1] Ewing, et al, MRM 2003. 50:283.

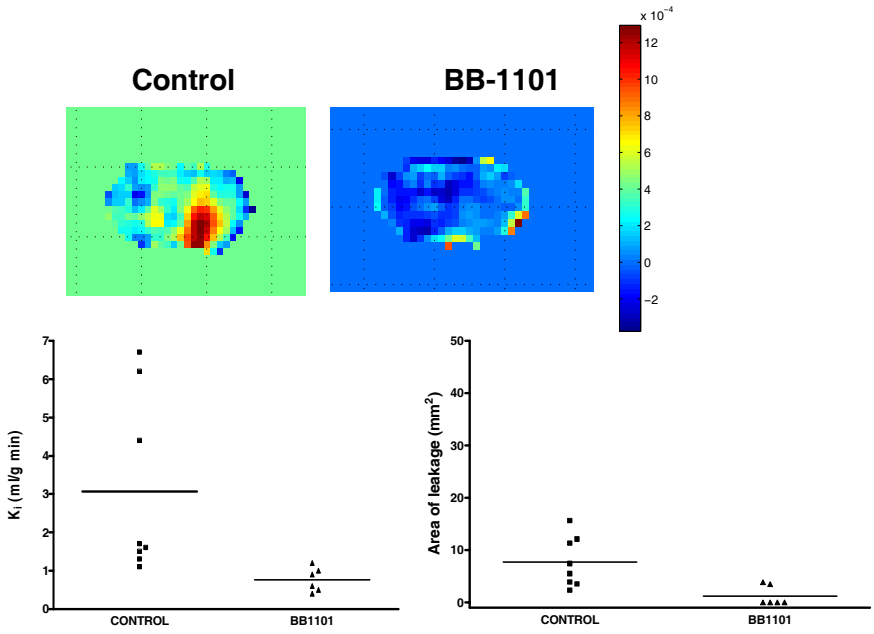

Fig. 1 Effect of BB-1101 on BBB permeability. Top row shows permeability color maps for control and treated rats. Bottom row shows plot of permeability values (left) and area of leakage (right) in control and treated rats.

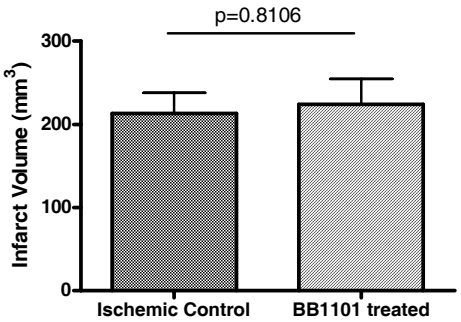

Fig. 2 The MMP inhibitor BB-1101 fails to reduce infarct size assessed after 48 h of reperfusion following 2 h of MCAO.