Transient increased permeability of the blood spinal cord brain barier after spinal cord injury in mice visualized using Gadolinium-enhanced MRI

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Introduction

The blood-spinal cord barrier (BSCB) preserves a highly regulated environment surrounding the spinal cord and prevents most intravascular substances from crossing and moving into this compartment. Recent experiments have shown that increased permeability of the BSCB occurs after spinal cord injury (SCI) in rats (1). This is of great importance for drug delivery in animal models of SCI since the time frame of increased permeability of the BSCB determines the therapeutic window. Experimental SCI therapy is increasingly evaluated in mice. So far, in vivo data on the response of mouse BSCB after SCI is not available. In this study we report our first data on mouse BSCB response to SCI.

Methods

SCI: 4 C57BL/6 mice were anesthetized using isoflurane 3% mixed with oxygen with a flow rate of 0.5 l/min. During the OP, isoflurane dose was lowered to 1.5% to maintain anesthesia. 3 mice were laminectomized at level Th 8/9 and the spinal cord (SC) was transected leaving only the ventral funiculus intact. 1 non-operated mouse served as control.

MRI: An injection of 1.0 mmol/kg Gd-DTPA-BMA (Gd) (Omniscan, Amersham Buchler, Braunschweig, GER) was injected in the tail vein. Contrast agent was applied 15, 60 or 120 minutes after SCI. For baseline signal we measured 1 non-operated mouse before and after Gd application. Imaging was performed 5 minutes after i.v. injection of Gd. The animals were anesthetized as described above. Experiments were performed using a 1.5 T MR system (SIEMENS, Erlangen, GER) and a dedicated animal volume resonator using a 3D-FLASH imaging sequence with the following parameters: TR/TE 14.0/5.22 ms, flip angle 30º, 28 partitions, partition thickness: 0,5 mm, FOV 80 mm, matrix size 512 x 512, voxel size 0.15 x 0.15 mm, 8 averages. The experiment was performed in sagittal plane for positioning and in axonal plane for detailed spinal cord imaging. Total imaging time was 20 minutes.

Data processing: Images were evaluated using the Syngo software package (SIEMENS, Erlangen, GER). In the operated animals the partition showing the lesion was selected and a ROI was placed over the spinal cord (excluding large vessels) and mean signal was calculated. A second ROI was placed within the FOV outside the animal contours for noise measurement. SNR was calculated dividing the mean signal in the SC through the mean signal in the outside ROI This procedure was performed for each of the 4 animals and repeated for several slices adjacent to the lesion.

Results

Fig.1 A/B shows images of the same non-operated mouse before (A) and after (B) Gd injection. After Gd injection vessels surrounding the SC show clear contrast enhancement but no enhancement inside the SC is present. Fig. 1 C and D show enhancement in the injured SC. Strong enhancement is present in the SC of the animal injected 15 min. post-OP (C). The animal injected 60 min post-OP (D) shows reduced enhancement compared to the animal injected 15 min. post-OP.

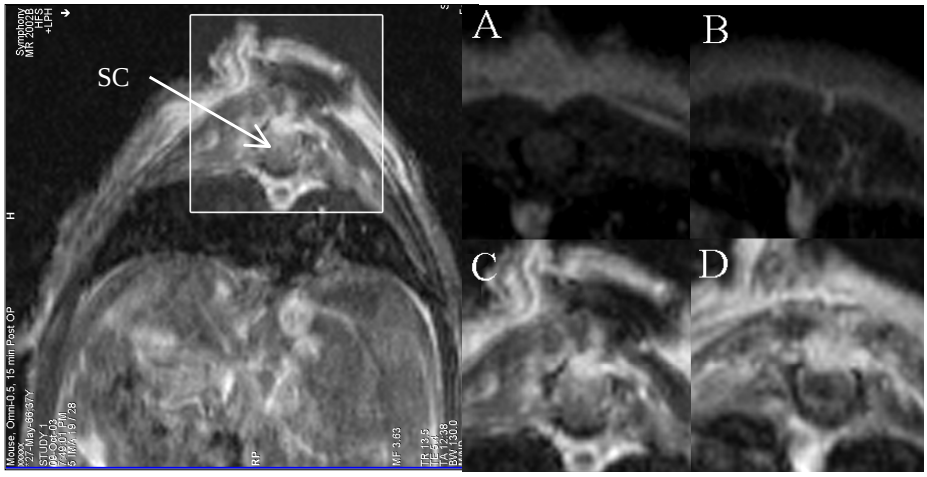

Fig. 1:Transversal T_1- weighted image of the body of the mouse (left) and enlarged SC area (A-D)

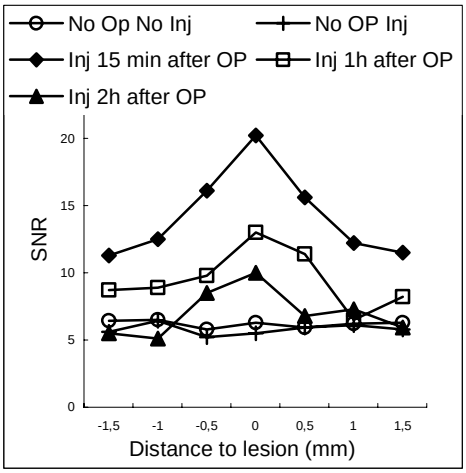

Fig. 2: SC SNR at the lesion (0) and adjacent slices

Fig. 2 depicts the SNR in the SC at the lesion epicenter (see Fig. 1) and three slides to both sides of this position. SNR in the 15 min. animal is 4 times the baseline signal and twice as high as that in the animal injected after 60 minutes. Compared to the animal injected after 120 min. signal increase is threefold. There is no SNR difference in the SC of the non-operated mouse before and after Gd injection.

Discussion

In this study we present preliminary evidence of a temporary increased permeability of the BSCB after SCI in mice. Compared to data on the response in rats (2) our data indicate that this increased permeability after SCI is more transient in mice, spanning approximately 4 hours compared to 3 to 4 days in rat. This is important because the therapeutic window for anti SCI drugs in mice seems to be considerably shorter than in rats. Further investigation of the temporary BSCB permeability in mice is required to evaluate the long-term effect of SCI on mouse BSCB to be able to optimize SCI drug treatment.

References

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