MEMRI Detects Axonal Degeneration Earlier then DTI

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Introduction Manganese (Mn^{2+}) Enhanced Magnetic Resonance Imaging (MEMRI) is a widely used imaging modality to study neuronal connectivity of the nervous system. Several studies have shown that Mn^{2+} enters cells through L-type voltage gated calcium channels and is transported along microtubules (1, 2). Thus, impaired axonal transport would manifest as a decrease in transport of Mn^{2+} detectable with *in vivo* MEMRI. Since axonal transport deficits usually occur prior to the histology-detectable axonal damage, MEMRI has the potential to detect early axonal damage.

In previous study (3, 4), the optic nerve degeneration resulting from retinal ischemia was delineated temporally using diffusion tensor imaging (DTI). The data showed that DTI could not detect damage in optic nerves until 3 days after retinal ischemia, at which time severe axonal damage was detected as decreased axial diffusivity. In this study, we conducted MEMRI at 1-2 days after retinal ischemia. We demonstrate that while axons appeared normal on DTI, there is loss of axonal transport as detected by MEMRI.

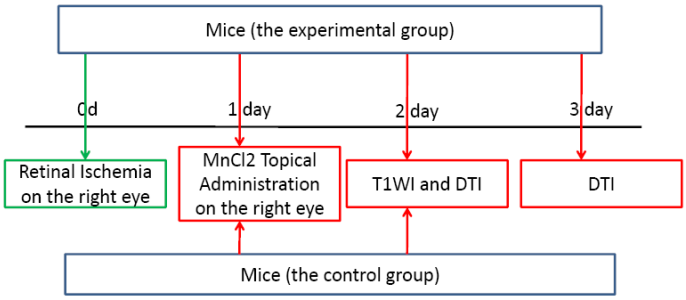

Fig. 1 Timeline of experimental procedures

Materials and Methods The timeline of experimental procedures was shown in Fig. 1. Briefly, five C57BL/6 female mice, 6 – 8 weeks of age underwent transient retinal ischemia on the right eye (3, 4). One day after ischemia, 10µl of 1.0 M $MnCl_2$ was placed on the right eye under anesthesia (Eye-Drop MEMRI, references 5 and 6). After 1 hour, the remaining solution was carefully removed by lint free tissue without touching the eye, and mice were returned to their cages. $MnCl_2$ was also provided to age-matched healthy mice using the same procedures. Twenty-four hours later, mice were anesthetized with a mixture of oxygen and isoflurane using an isoflurane vaporizer. Core body temperature was maintained at 37°C using warm water circulating in a pad. Mice were placed in a holder to immobilize the head. A 3-cm inner diameter solenoid volume coil was used to collect data in Bruker 11.7T small animal MRI. T_1-weighted imaging (T_1WI) was collected with TR 0.3 s, TE 29 ms, NEX 8, slice thickness 0.6 mm, field-of-view 2 cm, and data matrix 128 × 128 (zero filled to 256 × 256). DTI was collected with TR 2.5 s, TE 29 msec, Δ 20 msec, δ 3 msec, and six-direction diffusion scheme with b-values of 0 and 1 ms/µm^2. Axial diffusivity, radial diffusivity, and relative anisotropy (RA) were derived from DTI on a pixel-by-pixel basis. T_1WI and DTI indices were measured from left and right optic nerves. The intensity of T_1WI was normalized with the reference signal measured from a water phantom.

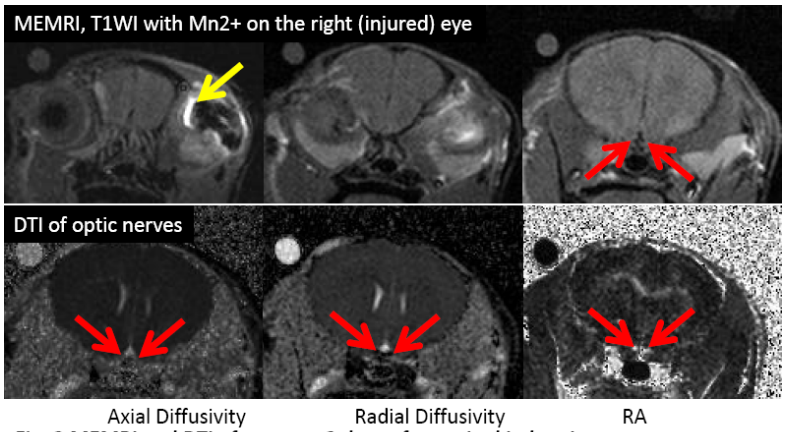

Fig. 2 MEMRI and DTI of a mouse 2 days after retinal ischemia

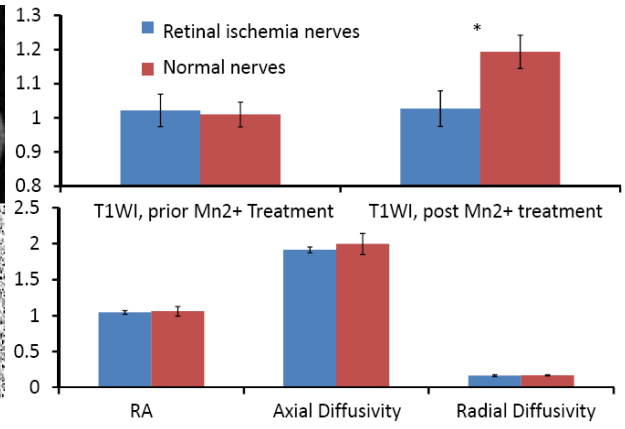

Fig. 3 MEMRI (T1WI) and DTI of optic nerves 2 days after retinal ischemia

Results In healthy mice, Mn^{2+} administration resulted in a significant 20% signal enhancement in normal optic nerves. As for the retinal ischemia mice, enhanced signal was found in retinal layers (a yellow arrow in Fig. 2), but not in the optic nerves (red arrows in fig. 2). Along with MEMRI, DTI was also performed (Fig. 2 and 3) but could not detect optic nerve damage at this time point (2 days after retinal ischemia). At 3 days after ischemia, a significant 43% decrease of axial diffusivity was measured in optic nerves (data not shown) in suggestive of axonal, which is in consistent with previous studies (3, 4).

Discussions and Conclusions

In this study, the sensitivity of DTI and MEMRI were compared for detection of axonal damage in optic nerves after retinal ischemia. Our data show that while optic nerves appeared normal on DTI index maps at 2 days after ischemia, MEMRI is able to detect axonal transport deficits. At 3 days after ischemia, DTI was able to detect the damage with a significant decrease of axial diffusivity in optic nerves, which is consistent with previous studies (3, 4). Our data suggest that MEMRI, which provides information about neuronal functionality, may serve as a sensitive imaging marker to detect axonal damage earlier than other imaging modalities.

References

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