Biweekly Repeated Topical-Loaded Manganese-Enhanced MRI in Mouse Visual System for Three Months

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Introduction

We previously demonstrated the feasibility of using a topical loading as an alternative approach of the traditional intravitreal injection to provide Mn2+ solution for MEMRI in the mouse visual system (1). We demonstrated that with a drop of 1 M MnCl2, significant signal increments were found within from retina to superior colliculus. The signals reached the peak in 1 day and returned to the baseline within 7 days. To evaluate whether the topical loaded MEMRI is feasible in a time course study, in this project, topical loaded MEMRI was performed biweekly for 14 weeks (3 months) in normal mice.

Materials and Methods

23 8-week-old female C57BL/6 mice were used. 1.0 M $MnCl_2$ solution was prepared in 1 M PBS and saline (Group 1, N = 6) or in distilled and deionized water (DI water, Group 2, N = 5). We found that although the solution appeared pH of 7 when it was made, both became slightly acidic (pH ~ 6) in 1 day (sealed, room temperature) before conducting the topical loading on animals. We further prepared 1.0M MnCl2 in DI water with NaOH to adjust pH before the topical loading (Group 3, N = 6) or used fresh-prepared 1.0M MnCl2 in DI water (Group 4, N = 6). For the topical administration, 5 µl 1.0M $MnCl_2$ was provided to the surface of the right eye on each mouse. After one hour, the remaining solution was carefully removed by lint-free tissue. At 24 hours after administration of MnCl2, T1WI was taken using a Bruker 4.7T BioSpec animal scanner with TR of 250 ms, TE of 8 ms, FOV of 1.5cm, and data matrix of 128 x 128 (with zero-padding to 256 x 256). The topical loaded MEMRI was conducted biweekly for 14 weeks (~ 3 months). ROIs were selected from retina, optic nerves, superior colliculus of left and right hemispheres, and reference (**Fig. 1**). At the end of MEMRI time courses, DTI was performed with TR 3 s, TE 29 ms, and a six-direction diffusion scheme with b-values of 0 and 0.85 ms/µm^2. Relative anisotropy (RA), Axial Diffusivity (AD), Radial Diffusivity (RD), and Trace (TR) were quantified.

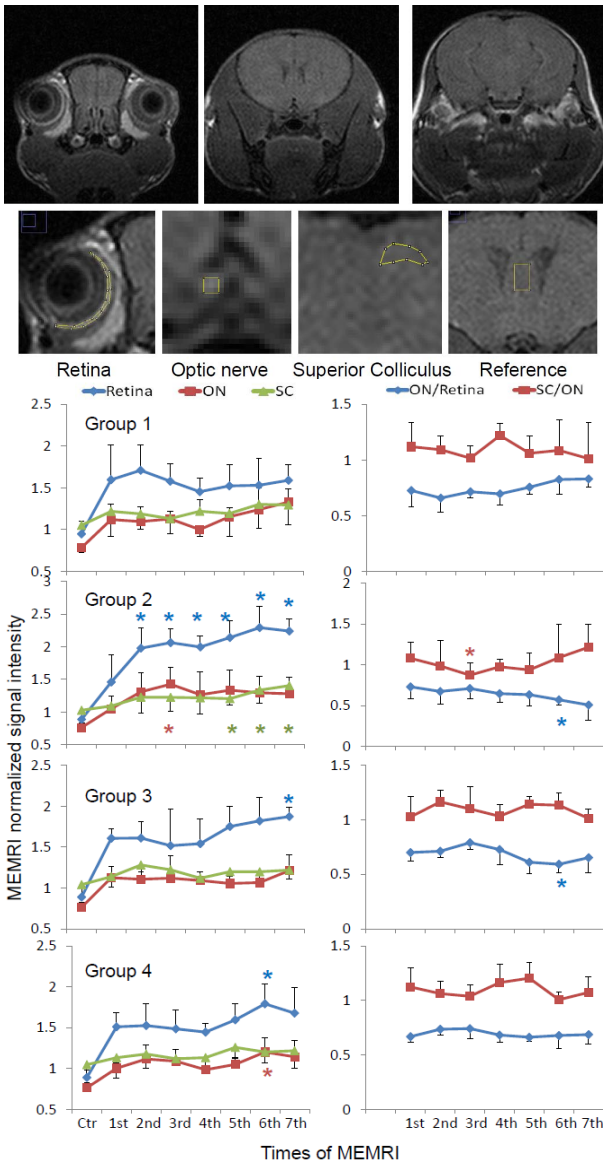

Figure 1. Biweekly MEMRI for 14 weeks. All MEMRI measurements showed significant increases as compared to the control signals. *: $p < 0.05$ compared to the 1st MEMRI.

Results

MEMRI showed enhanced signal in ipsilateral retinal and optic nerves up to contralateral superior colliculus (**Fig. 1**). Repeated performances of MEMRI showed consistent and reproducible measurements in Groups 1, 3, and 4. In Group 2, the 2nd – 7th MEMRI showed twice increments in retina as compared to its 1st MEMRI. At the end of MEMRI time course, one mouse in Group 2 (**Fig. 2**) showed decreased RA, decreased AD and increased RD, suggesting retinal damage.

Discussion and Conclusion

Topical loaded MEMRI is applicable in a time course study to produce a consistent and reproducible outcome. However, repeated exposure to Mn2+ may induce damage to retina. One mouse in Group 2 showed significant optic nerve damage detected by DTI.

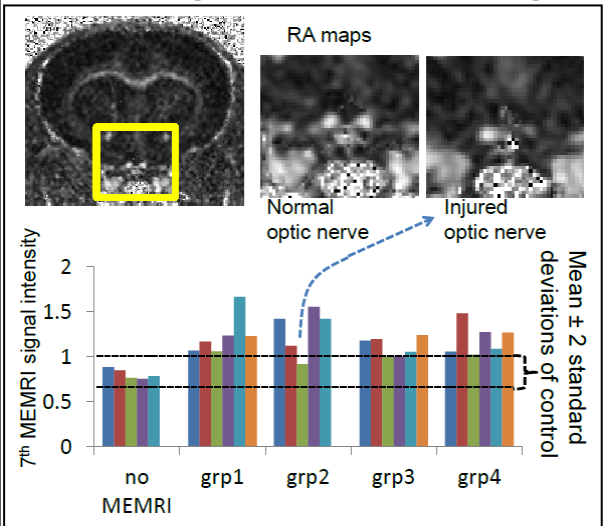

Figure 2. Reduced MEMRI correlated with optic nerve damage detected by DTI.

References

(1) Sun et al, IOVS, 2011; 52: 3914–3920.

Acknowledgement

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