Comparing Topical Administration and Intravitreal Injection of Mn2+ for MEMRI on Mouse Visual Pathway

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Introduction

Mn^{2+} Enhanced MRI (MEMRI) is a powerful tool to evaluate the retinal ganglion cells (RGCs) and their axonal conductivity. To deliver Mn^{2+} solution for RGC uptake, a small amount of Mn^{2+} has to be injected into intravitreal space (1, 2). To minimize the possibility of causing subconjunctival hemorrhage or trauma to the sclera, non-intrusive delivery methods, including the topical administration (3), transscleral iontophoresis, and transcorneal iontophoresis (4), have been proposed to minimizing the adverse effects from the procedures of Mn^{2+} loading. In this study, topical administration and intravitreal injection approaches were evaluated and compared on mouse visual system.

Materials and Methods

8-week-old female C57BL/6 mice were anesthetized by 1.2% isoflurane/oxygen. Body temperature was maintained using an electric heating pad. For the topical administration groups, 5 µl $MnCl_2$ with concentration of 0.5M (n=5), 0.75M (n=7), 1.0M (n=6), or 1.5M (n=7) 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 (Kimwipes, Ontario, Canada). For the intravitreal injection groups, 2 µl $MnCl_2$ with concentration of 1.0M (n=5) were injected into the vitreous space of each mouse. Mice were returned to the original cages. At 24 hours after administration of MnCl2, mice were anesthetized for imaging. The core body temperature was maintained using warm water circulating in a pad. A 7-cm inner diameter Bruker volume coil was used as a transmitter, and a 2-cm surface coil was used as a receiver. T1-weighted spin-echo imaging (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). Regions of interest (ROI) were selected from retina, optic nerves, and superior colliculus of left and right hemispheres. Signals from frontal cortex and water tube were used as internal and external references respectively. ROIs were manually delineated based on a co-registered T2-weighted RARE image. The measured intensity of each ROI was normalized by the internal reference signal.

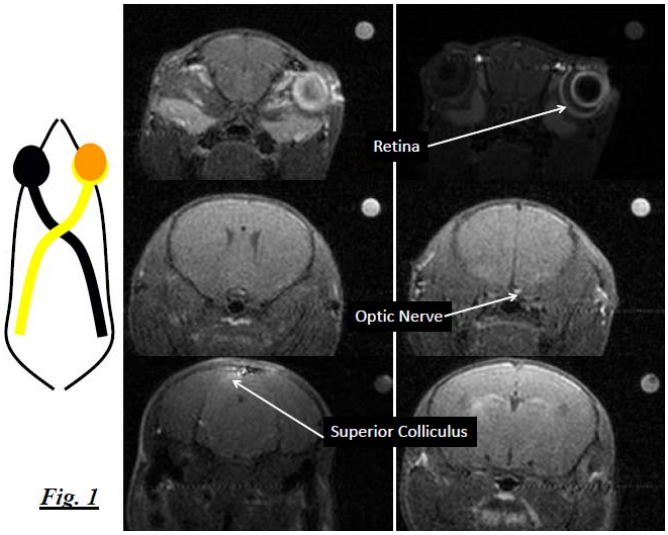
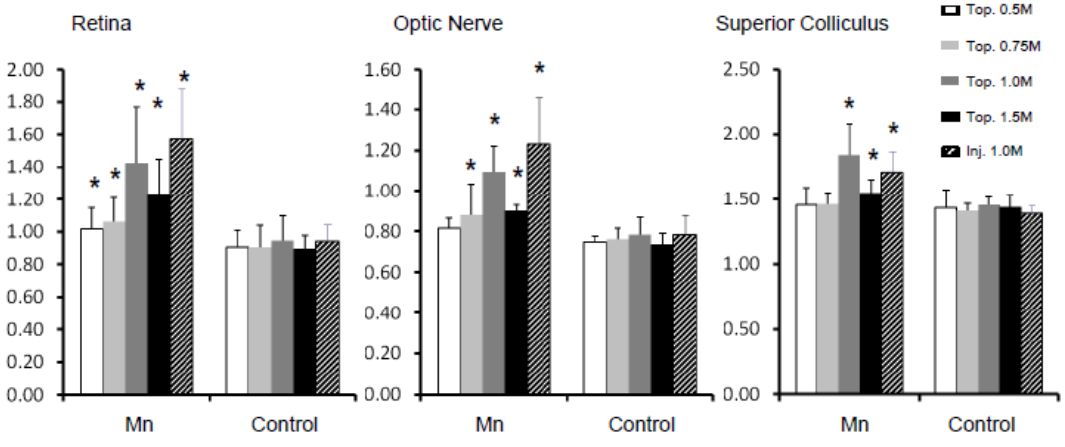


Fig. 1

Results

One day after Mn^{2+} administration, enhanced signal was seen in ipsilateral retinal and optic nerves up to contralateral superior colliculus (**Fig. 1**, 1M $MnCl_2$ topical administration). For the Mn^{2+}-affected ROI (right retinas, right optic nerves, and left Superior Colliculus), the enhancement ratios depended on the concentration of $MnCl_2$ provided on the eye. The higher concentration of $MnCl_2$ solution provided higher signal increase except the signals from 1.5 M group, which had signals lower than the data of 1 M group (**Fig. 2**). Comparing the topical administration with the intravitreal injection (both with 1 M $MnCl_2$), both showed significant signal increments in the visual system with no significant difference.



Discussion and Conclusions

This study demonstrated the possibility of using simple topical administration to perform MEMRI on the mouse visual system in vivo. Significant signal enhancement was seen in the entire visual system from the retina to the Superior Colliculus one day after topical administration of 1 or 1.5 M of $MnCl_2$, while lower concentration of $MnCl_2$ (0.5 and 0.75 M) showed significant enhancements in the retina and optic nerves but not the entire pathway. The enhancements peaked on day one, decayed on day two, and returned to the baseline on day seven. Our immunohistochemistry showed no axonal damage in optic nerves after 1M and 1.5M $MnCl_2$ topical loading. Topical administration of Mn^{2+} provided similar MEMRI to the data that observed with an intravitreal injection. Topical administration may serve as an easy and less invasive approach to load Mn^{2+} for MEMRI to analyze the visual system.

References (1) Pautler RG, NMR Biomed 2004;17:595-601. (2) Lindsey JD, Neuroimage 2007;34:1619-1626. (3) Sun et al, ISMRM 2008: 2320. (4) Li K, Investigative Ophthalmology & Visual Science, 2004, 45, 4, 1224-1231.

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