Toxicity of Mn^{2+} in MEMRI with topical loading

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Introduction

Manganese enhanced MRI (MEMRI) has been widely applied to investigate axonal transport in the rodent visual pathway. Intraocular injection is an established approach for $MnCl_2$ loading. Bearer et al. [1] have reported the impaired visual evoke potential (VEP) at the lowest intraocular dose allowing detectable MEMRI effect. In a recent report, the noninvasive topical $MnCl_2$ loading [2] was demonstrated without the need of invasive intraocular injection of $MnCl_2$. However, the effect of topical $MnCl_2$ loading on visual function was not evaluated. In this study, the toxicity of $MnCl_2$ was evaluated by visual acuity (VA) measurement [3,4] as well as optic nerve and retina MRI.

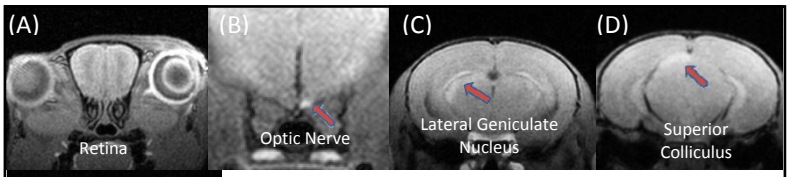

Fig. 1 Four representative axial images from 3D T1W data set one day after 0.75 M $MnCl_2$ loading. Visual pathway was enhanced from (A) right retina, (B) right optic nerve, (C) left lateral geniculate nucleus, and (D) left superor colliculus ; (E) oblique T1W image that included retina and optic nerve showed Mn^{2+} enhanced signal at right side.

Material and Method

Four groups of female C57BL/6 mice at 8 weeks of age were examined: control (n=4), 0.5 (n=4), 0.75 (n=6), and 1 M (n=5) of $MnCl_2$ loading. Mice were anesthetized using 1.5% isoflurane/oxygen for topical loading of 20µl of $MnCl_2$ on the right eye. An additional 20µl of $MnCl_2$ was applied every 20 min to compensate the volume loss due to evaporization. The body temperature was maintained at 37 ºC during loading with an electric heating pad. After an hour, a lint free tissue was used to remove the solution. Twenty-four hours after loading, mice were anesthetized and imaged on a 4.7 T animal scanner using a 3D gradient echo sequence with the following parameters: TR 15ms TE 2.63ms, flip angle 20, number of averages 16, FOV 15 × 15 mm^2, and matrix size 128 × 128 × 64 (zero-filled to 256 × 256 × 64). Region of interest (ROI) included retina, optic nerve (ON), and superior colliculus (SC). Visual acuity (VA) was assessed daily from 1 to 7 days. Optic nerve were imaged on 4.7 T animal scanners with multiple-echo spin-ehco diffusion weighted sequence at days 1 and 7 with the following parameters: TR 1.5s, TE 34 ms, inter-ehco delay 19 ms, FOV 22.5 × 22.5 mm^2 , matrix size 192 × 192 (zero-filled to 384×384), thickness 0.5 mm. Retina images were performed on an11.74 T scanner with a standard spin echo sequence with the following parameters: TR 2s, TE 34ms FOV 12 × 12 mm^2 matrix size 256 × 256 (zero-filled to 512 × 512).

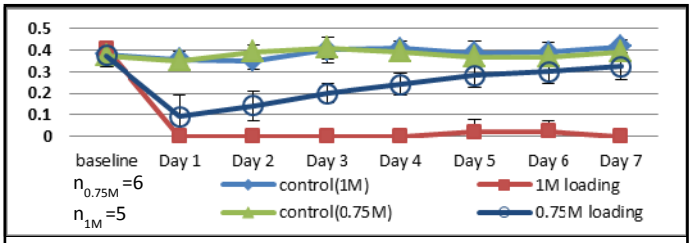

Fig. 2 Visual acuity (VA) time course after 0.75 and 1 M $MnCl_2$ loading on right eyes. VA irreversibly decreased from normal (0.4) to complete blind (0) after 1 M loading. VA decreased to 0.1 (not completely bind) and recovered at day 5 after 0.75 M loading.

Results & Discussion

At one day after 0.75 and 1 M $MnCl_2$ loading on right eyes, significant T1W enhancement was seen in the right retina, right optic nerve, left lateral geniculate nucleus and left superior colliculus (Fig. 1). Only slight enhancement of retina was seen in mice loaded with 0.5M $MnCl_2$. Significant visual function impairment was seen in both 0.75 and 1 M $MnCl_2$ loaded eyes (Fig. 2). Upon 1 M $MnCl_2$ loading, irreversible VA decreased from normal (VA = 0.4) to complete blindness (VA = 0) from 1 day after loading. In 0.75 M $MnCl_2$ loaded eyes, VA decreased to 0.1 (not completely blind) at 1 day after and recovered to approximately the normal range at 5 days after loading (Fig. 2). There was no detected axonal or myelin injury in optic nerve loaded with 1M $MnCl_2$ at 1 and 7 days after loading (Fig. 3). However, a significant reduction in retinal thickness (~27% compared to the control) was seen in eyes loaded with 1M $MnCl_2$ (Fig. 3).

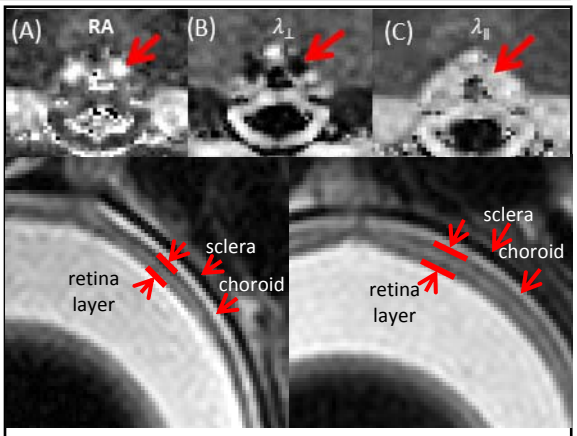

Fig. 3 DTI parameters of optic nerve, indicated by the arrow, in (A) RA, (B) radial, and (C) axial diffusivity maps after 1 M $MnCl_2$ loading at the right eye were not affected. T2W images showed that the right retina (D) after 1 M $MnCl_2$ loading was thinner than the control retina (E). Thickness decreased by 27 % after $MnCl_2$ loading.

Conclusion

Our data suggested that although topical loading of 1 M $MnCl_2$ did not injure optic nerve, as indicated by normal DTI parameters, the damaged retina was likely responsible for the irreversible loss of vision. The reduced retinal thickness may reflect the loss of retinal cells. The success in optic nerve enhancement after loading may suggest the retinal ganglion cells were not lost and still capable of uptake Mn^{2+}. Alternately, the retinal ganglion cell was damaged after uptake of Mn^{2+} and transporting to its axon. This is the first time retinal integrity was assessed after $MnCl_2$ loading.

Reference

[1] Bearer *et al*., Neuroimage, 2007, 37(suppl 1) S37-S46; [2] Sun *et al*., IOVS, 2011, 52: 3914-3920. [3] Prusky *et al.*, IOVS, 2004, Vol: 45 No.12; [4] Douglas *et al.*, Visual Neuroscience, 2005, 22, 677-684