Topical administration of Mn2+ for MEMRI may not enter vitreous space to reach retina

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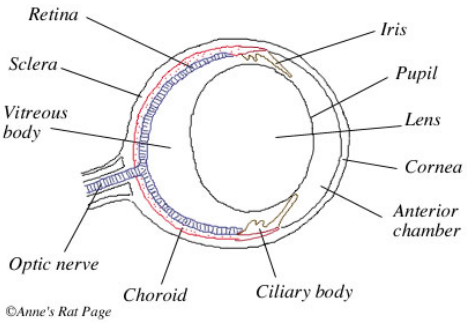
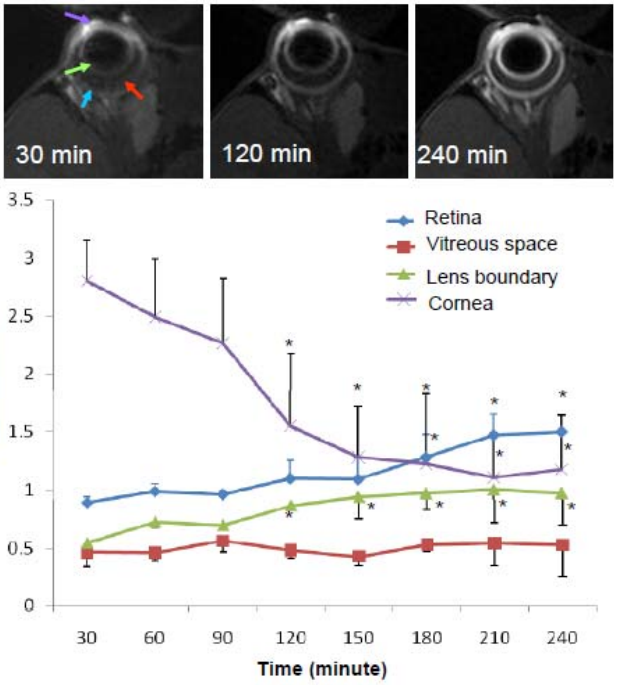
Introduction

Mn^{2+} Enhanced MRI (MEMRI) is a powerful tool to evaluate the retinal ganglion cells (RGCs) and their axonal conductivity. Our team has previously demonstrated the feasibility of using non-invasive topical loading of the $MnCl_2$ on the surface of eye as an alternative to intravitreal injected (1, 2, 3), which has been commonly used to deliver Mn^{2+} solution for RGC uptake. We have demonstrated that topical loading of 1.0M $MnCl_2$ is efficient enough leading to 20 – 50% signal enhancement in the visual system from retina up to superior colliculus. However, it is not clear how a topical drop of $MnCl_2$ traveled from the cornea to the retina. In this study, high resolution T1-Weighted Imaging of the eye was repeatedly acquired every 30 minutes in the initial 4 hours after MnCl2 (1 M) loading.



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 1.0M (n=5) 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). Mice were placed to the home cages for recovery for 20 minutes. For imaging, mice were anesthetized by 1.2% isoflurane/oxygen. 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 cm, and data matrix of 128 x 128 (with zero-padding to 256 x 256). One sagittal image cutting cornea and optic nerve head was repeatedly acquired in every 30 minutes for four hours. Regions of interest (ROI) were selected from cornea, retina, vitreous space (or called vitreous body), lens boundary. The atlas figure (**Fig. 1**) was copied from website (http://www.ratbehavior.org/Eyes.htm). The fat tissue behind the eye ball was used to serve as the internal reference signal.



Results

The signal intensity of cornea (purple arrow in **Fig. 2**) gradually decreased, suggesting the release of $MnCl_2$ into the ocular space. Interestingly, no significant change occurred in the vitreous space. In contrast, noticeable increments of signal were found in the retina and lens border. In 240 minutes after the $MnCl_2$ induction, the retina signal increased 70% ($p < 0.05$), and the lens border signal increased 80% ($p < 0.05$). These data suggest that the uptake of Mn^{2+} did not diffuse across cornea or sclera into vitreous space, but by means of the focal capillary circulation, which carries Mn^{2+} directly to the retina.

Discussion and Conclusions

In addition to the topical administration for MEMRI for visual system proposed early from our group, another non-invasive loading approach, the transscleral or transcorneal iontophoresis (4) have been used and shown to be an efficient non-intrusive delivery method for loading Mn^{2+} into vitreous space. Iontophoresis has been applied to deliver a compound across a membrane by the assistance of an electric field. Without the electric driving force in our proposal, it is not clear how external Mn2+ may reach RGC after a topical drop. We suspected that the concentration gradients of ions may drive Mn^{2+} diffusing across the corneal or sclera into vitreous space, which could later reach the retina for the signal enhancement seen in retina and optic nerve. But the results surprised us. The signal intensity of vitreous space did not change over a period of 4 hours after the topical loading, despite the gradual changes in retina. Noticeable increment of signal was found not only in the retina but also in the lens boundary. The lens boundary is composed of epithelial cells, which have blood supply from the anterior ocular circulation. It is possible that topically applied Mn^{2+} may enter anterior vascular circulation, perhaps through the sclera venous sinus (canal of Schlemm) and iris capillaries, which exchanges fluid with the capillary circulation involved in the lens boundary and retina. Worth noting is the fact that the propagation of Mn^{2+} was retrained within the applied eye. There was no detectable signal change in the retina, optic nerve, and Superior Colliculus in the hemisphere opposite to the hemisphere with Mn^{2+} affection, regardless of the significant signal increments in the Mn^{2+}-affected visual system (data not shown).

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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