Manganese-Enhanced MRI for Preclinical Evaluation of Therapeutic Efficacy of Retinal Degeneration Treatment

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Purpose

Macular degeneration is a leading cause of blindness among adults. Currently, numerous therapies for this disease are being developed to maintain the balance of proteins and enzymes required for the visual cycle of phototransduction. Preclinical evaluation of the therapeutic efficacy of these drugs must demonstrate that both structure and function of the retina are intact in order to validate the ocular health of the treated animals. In this work, we have implemented a manganese-enhanced MRI (MEMRI) protocol for the eyes to evaluate both of these criteria in a single measurement. MEMRI generates functional maps of cellular activity *in vivo*[1] by imaging localized administrations of Mn^{2+}, a T1 contrast agent that is transported into the cytosol of actively signaling cells such as photoreceptors through calcium and other ion channels. Here, we have demonstrated that MEMRI is able to distinguish between intact, treated, and damaged retinas. Results are consistent with standard OCT, histology, and ERG methods and can be used as an alternative technique to evaluate therapeutic efficacy of drugs during preclinical development.

Methods

$Abca4^{-/-}/Rdh8^{-/-}$ double knockout mice[2] were divided into three experimental groups: no light illumination (NLI, no retinal degeneration; n=6), light illumination (LI, complete degeneration; n=4), and treatment with retinylamine[2] (Ret-NH_2, protection from light-induced degeneration; n=3). Retinylamine was administered by oral gavage (0.05g/kg) 16 hours prior to light illumination at 10,000 lux yellow light for 1 hour. OCT and ERG measurements were acquired one week after light illumination on separate days. MEMRI was performed the following week. For MEMRI, Mn^{2+} was administered directly to the eye by intravitreous injection of $MnCl_2$ (2.4µL, 5mM) into the right eye. The left side was not injected and served as a bilateral control. MR images were acquired two hours after Mn^{2+} injection on a preclinical 7T Bruker BioSpin scanner (Billerica, MA) equipped with a commercially available volume coil. T1-weighted images were collected using a 2D coronal spin echo acquisition (TR=400ms, TE=10.6ms, FOV=2.5x2.5cm, resolution=98x195µm, total imaging time=14min).

Results and Discussion

In MEMRI images, contrast enhancement was evident in the retinas of the NLI control and Ret-NH_2 treated mice, while little enhancement was observed in the LI mice (Figure 1a,b; *p<0.001, **p<0.00001). This data correlated well with OCT and histology findings of intact retinal structure in the NLI and Ret-NH_2 mice and loss of structure in the LI animals (Figure 1c,d). Likewise, MEMRI was in agreement with ERG data indicating normal light-responsive electrical activity in the NLI and treatment groups and low responsiveness in the LI mice (Figure 1e). Our results demonstrate that MEMRI is complementary to standard methods currently used to evaluate retinal health, and can be used to evaluate therapeutic efficacy of drugs in development for protection against retinal diseases.

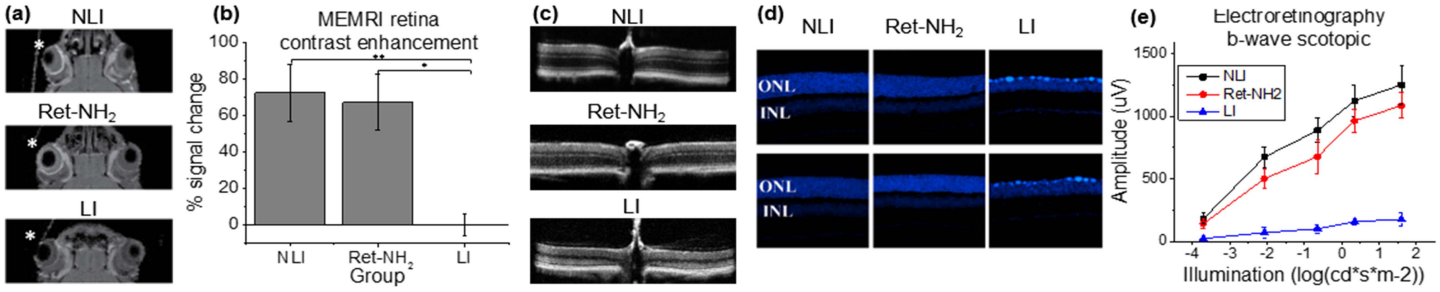

Figure 1. MEMRI enhancement of the retina two hours after injection into the right eye (*) demonstrates strong contrast media uptake in healthy and treated mice (a, b). These results correlate well with (c) OCT images, (d) histology, and (e) ERG results that distinguish between healthy and degenerated retinal structure and

References

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2. Maeda A, Golczak M, Chen Y, et al. Primary amines protect against retinal degeneration in mouse models of retinopathies. *Nat Chem Biol*. 2012;8(2):170–8.