Evaluation of the Applicability of Manganese-Enhanced and Dynamic Gadolinium-Enhanced Imaging to Study the Role of Caveolin-1 in Blood-Retinal Barrier Integrity

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Impact and Significance: Manganese enhanced MRI(MEMRI) has recently emerged as an important new tool in the study of the central nervous system by combining demonstrated clinical relevance(1), strong T1 relaxivity and a biodistribution uniquely coupled with the electrochemical state of the tissue of interest. As such, MnEMRI represents an attractive modality for the study of retinal function. The applicability of this technique to the field of ophthalmology is increasingly evident through various models of light/dark adaptation, impairment of retinal function by ouabain, blood-retinal barrier disruption by sodium iodate and a transgenic mouse model of diabetic retinopathy(2). In the present work, we seek to demonstrate the applicability of MnEMRI to study the involvement of caveolin-1 (Cav-1), an important caveolar membrane domain phosphoprotein, in the regulation of ionic homeostasis and blood-retinal barrier permeability using a cell-type-specific Cav-1 knock out mouse model. Gadolinium-enhanced dynamic imaging was also evaluated as an additional potential metric.

Methods: We used a 7T Bruker Biospin system with volume excitation and 6mm loop surface coil reception. In agreement with animal care procedures, Cav-1 ko or wild-type balb/c mice were maintained in a dark environment for 12hours or more (dark adapted) or in ambient light (light adapted), and were injected with 66mg/kg of manganese intraperitoneally 4 hours before imaging. Manganese-enhanced images (spin echo; TR/TE=450ms/17ms) of light or dark adapted mice were obtained at resolutions sufficient to outline several retinal layers (<30µm in-plane resolution). Reception field heterogeneity was partially restored by applying a modified version of an intensity-correction algorithm initially tailored for cardiac imaging(3). In addition, blood-retinal barrier function was assessed from dynamic contrast enhanced imaging data obtained on control or 30 mg/kg_{bw} intraperitoneal iodate-disrupted animals. Spin echo images (TR/TE=750/47ms, 78×54µm in-plane, repetition rate: 2 images/min) were acquired before and up to 20 min after bolus tail-vein injection of a 0.3mmol/kg_{bw} dose of gadolinium-DTPA.

Results: The use of a cross-coil setup with volume excitation and surface reception allowed the discrimination of 3 retinal layers in a light-adapted, manganese-injected mouse retina at 7T (figure 1). This setup may be used to study the involvement of various caveolin-1 pools in the ionic homeostasis of the light or dark-adapted retinal milieu. Dynamic contrast-enhanced MRI of the eye in iodate-injected wild type animals showed extensive leakage through the retina, associated with a very short residence time in the retinal compartment. Extensive contrast accumulation was observed in the vitreous and anterior chamber compartments (figure 2). Based on this maximally permeable BRB model, we estimate that under our experimental conditions, the detection of potential effects of a cell type-specific disruption in Cav-1 expression would require a signal enhancement at 17.5 min post-injection of 20% or greater in the vitreous and of 40% or greater in the anterior chamber.

Conclusions: MnEMRI and Gd-DCE imaging of the mouse retina at 7T represent attractive tools for the study of the involvement of caveolin-1 in the ionic homeostasis of the retina and in the blood-retinal integrity. Future studies will apply the experimental conditions presented here to three ocular cell-type specific caveolin-1 deficient mouse mutants.

References:

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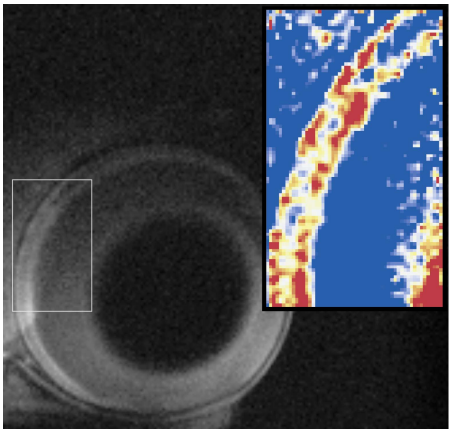

Figure 1: Mn-enhanced image of a light-adapted mouse eye (isotropic resolution=29µm, thickness=620µm). Inset: close-up of the retinal region highlighted (white box), displayed after reception field correction, zero-filling and change to a colored lookup table. The three retinal layers are clearly visible.

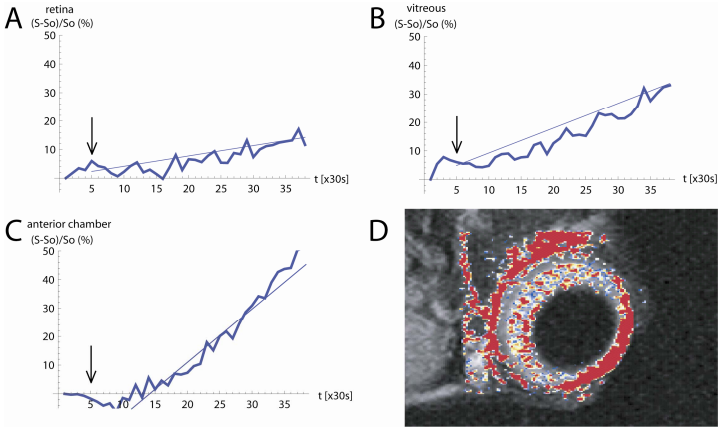

Figure 2: Signal enhancement (SE, %) over retinal (A), vitreous (B) and anterior chamber (C) compartments following gadolinium DTPA injection (arrows). A linear fit of the post-injection SE is displayed. D: overlay of a pre-injection spin-echo image with a pseudo-colored SE map. The SE map is tresholded from 10% (blue) to 50%(red), with out-of-bounds values left transparent.