MRI measurements of the morphology and vasculature of the mouse eye in vivo in control animals and models of diabetic retinopathy

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Introduction:

Mouse models of ocular diseases are becoming increasingly prevalent due to the availability of a large number of transgenic models which mimic conditions in humans. These models show either changes in retinal morphology, vascularity, or both. One example is diabetic retinopathy which is a severe complication in which blood vessels and neurological cells in the retina are damaged. In mild nonproliferative retinopathy areas of retina blood vessel swelling (microaneurysms) occur, moderate nonproliferative retinopathy is characterized by blocked vessels, severe nonproliferative retinopathy leads to abnormal vessel growth, and in proliferative retinopathy fragile vessels can leak which can lead to vision loss and blindness. Traditional measurements of morphology and/or blood flow either use planar optical techniques, or single-timepoint methods with fluorescent dyes. The goal of this work is to determine whether very high resolution magnetic resonance microscopy can detect morphological changes and/or abnormal vessel grow or the leakage of the blood vessels in mouse models, complementing a large body of work performed in rats [1] In this study the C57BL/6J Ins2Akita mouse model, which develops diabetic retinopathy at the age of ~6-9 months was studied.

Subjects & Methods:

Male C57BL/6 control and C57BL/6J Ins2Akita mice (25-30 g) were anesthetized using an isoflurane/oxygen mixture and placed in a home built animal handling system. Experiments were performed on a 14.1 tesla wide-bore magnet with Varian Direct Drive system using a custom built 8 mm diameter surface coil with balanced impedance matching. During the experiment, temperature and breathing were controlled with a small animal monitoring system (SA Instruments, NY). Two different orientations, one parallel and one perpendicular to the optical nerve were used to acquire high resolution images from the eye using a gradient echo sequence. The imaging parameters were: TR 200 ms, TE 8.56 ms, matrix size 192 x 264 (3/4 partial Fourier), field-of-view 6 x 8 mm, 16 averages, giving a total data acquisition time of 10.6 minutes. The in-plane resolution was 30 x 30 μm, with a slice thickness of either 200 or 100 μm. To study the vasculature of the eye a three dimensional time-of-flight gradient echo sequence was used (TR=40 ms, TE=5.5ms, NT=2, matrix: 128 x 132 (176) x 162, FOV= 5 x 7 x 6.5 mm^3, T_{exp} =26 minutes).

Results:

Figure 1(a) shows a representative image parallel to the optical nerve. The voxel size is about nine times smaller than previous studies [2], and enables clear delineation of different retinal layers which can be unambiguously correlated with histological images from reference [3]. It has been suggested that thinning of the retina occurs close to the optic nerve in diabetic rat retinas [4], and so we performed similar measurements, as shown in Figure 1(b). However, using four animals, statistically significant differences were not observed in the mouse model. Figures 1(c) shows an image from a wild type animal, acquired perpendicular to the optic nerve, and clearly delineates the vascular structure at the fundus of the eye. Figure 1(d) shows a three-dimensional MIP reconstruction from the TOF angiography sequence. Major blood vessels providing the inner retina as well as the outer eye with blood can be identified. These images represent the first MRI angiograms that have been produced from the mouse eye.

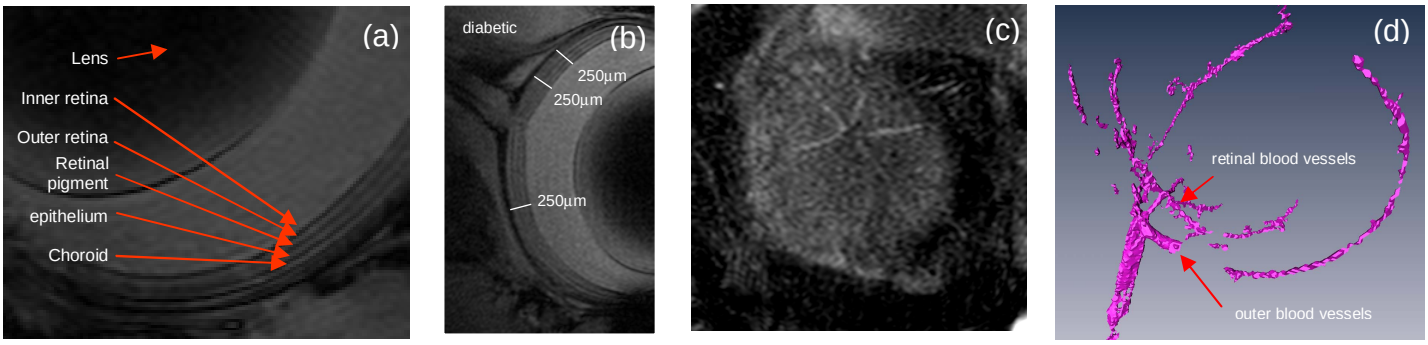

Figure 1: (a) Zoomed image parallel to the optical nerve. Retinal layers at the back of the eye can be distinguished and correspond directly to histological images [1]. (b) Measurement of the retinal thickness in a diabetic animal. (c) Fundus of the eye of a wild type animal. (d) MR maximum intensity projection angiogram of the major vessels in the mouse eye

Discussion:

High resolution *in vivo* microimaging using an optimized RF coil and animal handling system enables the clear delineation of different retinal layers in the mouse eye, and also visualization of the vascular system feeding the eye. Unlike in a rat model of diabetic retinopathy, no statistically significant difference between the retinal morphology of six month old C57BL/6J Ins2Akita mice and the wild type mice was seen. Future work will concentrate on improving measurements of intact and leaky vasculature using a blood-pool agent such as gadolinium-linked-albumin to attempt to detect signal enhancement in the blood vessels and possible leakage areas in the retina. Also, use of a more severe retinopathy model, such as oxygen induced retinopathy, is planned.

References:

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