QMT is Specifically Sensitive to Myelin and Not Axonal Injury in Optic Nerve from Mice Undergoing Transient Retinal Ischemia

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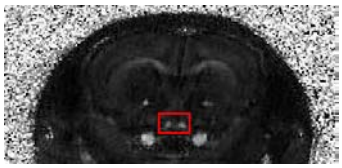
Introduction

Optic nerves from mice that have undergone retinal ischemia were examined using a newly implemented selective inversion recovery quantitative magnetization transfer (SIR-QMT) technique. Previously published results suggest that the optic nerve from retinal ischemia mice suffers significant axon degeneration without detectable myelin injury at three days after reperfusion. Ex vivo QMT parameters in fixed brain tissue samples from both shiverer mice (which have no myelin) and control mice that have undergone retinal ischemia were compared with diffusion tensor imaging (DTI) results. Our findings suggest that the QMT estimated ratio of the pool sizes of the bound and free water protons reflects the different myelin contents in the optic nerves between the shiverer and control mice. This pool size ratio is specific to myelin content only and is not affected by the presence of axon injury in mouse optic nerve three days after transient retinal ischemia.

Methods

Unilateral retinal ischemia was induced in five shiverer and six control mice by raising the intraocular pressure (IOP) of the left eye above the systemic arterial pressure for 1 hour followed by reperfusion. At three days after the retina ischemia, all mice were euthanized and perfused with phosphate-buffered saline (PBS) followed by 10% formalin/PBS solution. The fixed mouse brains were kept in 10% formalin/PBS solution and stored at 4°C for one week, then transferred to PBS solution before imaging. Fixed brains were placed in a 1cm inner diameter solenoid coil. For each brain, data from one coronal slice containing both optic nerves was acquired using a 4.7T Varian UNITY INOVA spectrometer. A fast spin echo sequence with a preceding inversion pulse was used for QMT measurements. 18 images with the inversion time ranging from 5ms to 7.9s were obtained with 2s constant predelay[1], 8 averages, 16 echoes, 10ms echo spacing time, 25mm by 25mm field of view, 0.8mm thick slice, and 256x256 data matrix zero-filled to 512x512. Data were fitted to a bi-exponential function of the inversion times to determine the pool size ratio pixel by pixel. A diffusion weighted spin echo pulse sequence with 1s repetition time, 38ms echo time, 13ms time between gradient pulses, 4ms diffusion gradient duration, b value of 1.879 $ms/\mu m^2$, diffusion sensitizing gradients along six directions (1,1,0)(0,1,1)(1,0,1)(-1,1,0)(0,-1,1)(1,0,-1), and the same spatial resolution as the QMT experiments was used to determine the axial and radial diffusivities at each pixel.

Results



The figure shows the relative anisotropy (RA) map of one coronal slice of a control mouse brain. Optic nerves are located inside the red rectangle. RA maps were used to determine the position of the optic nerves for each mouse. QMT and DTI parameters for optic nerves (each optic nerve ROI contains 15-20 pixels) were obtained from corresponding pool size ratio and diffusivity maps, and are listed in the table below.

	Pool size ratio		Radial diffusivity ($\mu m^2/ms$)		Axial diffusivity ($\mu m^2/ms$)	
	Left eye (injured)	Right eye (normal)	Left eye (injured)	Right eye (normal)	Left eye (injured)	Right eye (normal)
Control	0.102±0.011	0.099±0.014	0.17±0.03	0.17±0.03	0.49±0.09	0.67±0.07
Shiverer	0.069±0.003	0.077±0.007	0.22±0.02	0.22±0.04	0.53±0.05	0.73±0.06

Discussion

1) Control vs. shiverer mouse: The measured pool size ratio is roughly 30% smaller in the shiverer vs. control mice for both injured and uninjured optic nerves. The radial diffusivity of shiverer mouse optic nerves increases by roughly the same percentage comparing to that of control mice. These results support the notion that the pool size ratio, like the radial diffusivity, is sensitive to myelin.
2) Injured vs. control eye: It is important to know the specificity of the QMT pool size ratio to myelin sheath integrity. Previously reported histological results showed axonal damage without myelin injury in optic nerve from mice of transient retinal ischemia at three days after reperfusion. These conditions are reflected by decreased axial diffusivity without changes in radial diffusivity [2]. Our results are consistent with these previous findings. No significant changes in the QMT pool size ratio in optic nerves with axonal damage caused by retinal ischemia was seen in the present study. Our results suggest that the pool size ratio, one of the QMT parameters, is specific to myelin integrity.

References

1. Gochberg DF et al, Magn Res Med (2006), in press. 2. Song SK et al, NeuroImage 20, 1714-1722 (2003)

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