Evolving Optic Nerve Degeneration after retinal ischemia Assessed Using MR Diffusion Tensor Imaging

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Introduction

The mouse model of retinal ischemia, induced by high intraocular pressure, has been widely employed for studying pathologic mechanisms underlying human glaucoma and hypertension. Transient retinal ischemia/reperfusion causes an acute inner retinal degeneration (1, 2) with axonal degeneration in optic nerve. Subsequent to this retinal degeneration, secondary myelin fragmentation has also been found ("Wallerian degeneration") (3).

Magnetic resonance diffusion tensor imaging (DTI) provides a non-invasive tool to examine the structural changes in white matter. Previous studies have demonstrated that directional diffusivities, $\lambda_{\parallel}$ and $\lambda_{\perp}$, derived from DTI are capable of characterizing the short-term evolution of optic nerve degeneration after retinal ischemia (4). The findings indicate that the initial decrease of $\lambda_{\parallel}$ correlates with axonal injury validated with neurofilament SMI-31 immunostaining. The secondary myelin fragmentation was associated with increased $\lambda_{\perp}$ and was verified with myelin basic protein immunostaining.

In this study, DTI was used to evaluate the long-term evolution of the optic nerve degeneration following transient retinal ischemia. DTI examination of optic nerves of mice was performed from 1 to 120 days after reperfusion.

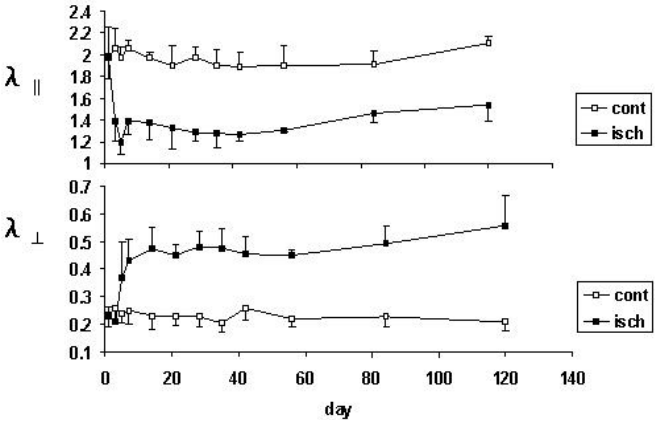
Materials and Methods

Retinal ischemia

The intraocular pressure (IOP) of the left eye of each mouse was raised above systolic blood pressure by cannulation of the anterior chamber with a 32-gauge needle connected to a saline reservoir placed above the eye. The applied pressure of 110 – 120 mmHg is in the range or slightly above systemic systolic blood pressure in mice. The elevated IOP was maintained for 65 minutes. Ischemia was confirmed by ophthalmoscopic observation of the blanched fundus. The contralateral eye, which serves as the control, was not cannulated. Reperfusion started immediately after removal of the cannula.

DTI of mouse optic nerve

Seven male Swiss Webster mice underwent IOP elevation and serial longitudinal DTI examination at Days 1, 3, 5, 7, 14, 21,28, 35, 42, 56, 84, and 120days after reperfusion. All DTI experiments were conducted in an Oxford Instruments (4.7 T, 33 cm clear bore) magnet equipped with a 15 cm inner-diameter actively shielded Oxford gradient coil (180 mT/m, 200 μsec rise time). The 6-direction DTI (5, 6) acquired with the following acquisition parameters: TR: 0.75s TE: 50s, Δ: 25 msec, δ: 10 ms, slth: 0.5 mm, FOV: 1.5 cm, data matrix 128×128 (zero filled to 256× 256), and b-value = 764 sec/mm^2. Five coronal slices of mouse brain were collected between 0.5 to 2 mm of bregma. DTI indices including relative anisotropy (RA), Tr(D), $\lambda_{\parallel}$, and $\lambda_{\perp}$ were measured in the optic nerve.



Results and Discussion

The current study presents the extended time course describing optic nerve degeneration after retinal ischemia. Serial measurements of $\lambda_{\parallel}$ and $\lambda_{\perp}$ obtained from the seven mice obtained serially from 1 to 120 days after reperfusion are presented in Fig. 1. There were no discernible differences in all DTI parameters between the control and the injured optic nerves on day 1 after ischemia. The $\lambda_{\parallel}$ decreased significantly in the injured optic nerve by day 3 after ischemia. The value of $\lambda_{\parallel}$ reached its minimum on day 5 after ischemia. An upward trend in $\lambda_{\parallel}$ at days 7 to 120 can seen. However, $\lambda_{\parallel}$ never returned to the control level. The $\lambda_{\perp}$ slightly decreased in the optic nerve of the injured eye on day 3 after ischemia. However, $\lambda_{\perp}$ elevated significantly beginning at day 5. It reached a plateau at about day10 (~ 200% of the control value). Only a minor upward trend was seen beginning after day 60.

In most CNS injuries such as MS and stroke, the water diffusion coefficient is significantly elevated with concomitant decrease in anisotropy in the chronic stage. This has been interpreted to reflect the tissue disintegration at the chronic stage. However, the current study clearly demonstrates that water diffusion in optic nerve degeneration after retinal ischemia does not behave as those observed in MS or stroke in the examined time period. The present study does not clarify cellular and sub-cellular changes occurring over the time course of optic nerve degeneration. Detailed histological studies of the injured optic nerves will be necessary to understand the underlying mechanisms reflected by the directional diffusivities.

Reference

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