Axonal Damage Caused by Exposure of Axon Terminals to Amyloid Beta

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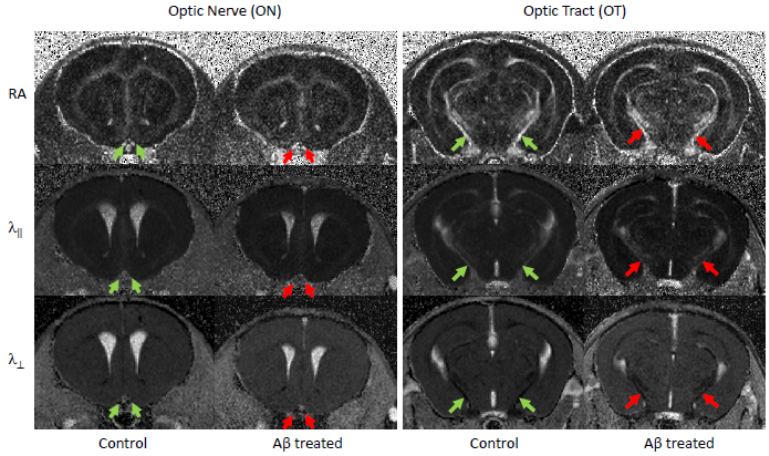
Introduction

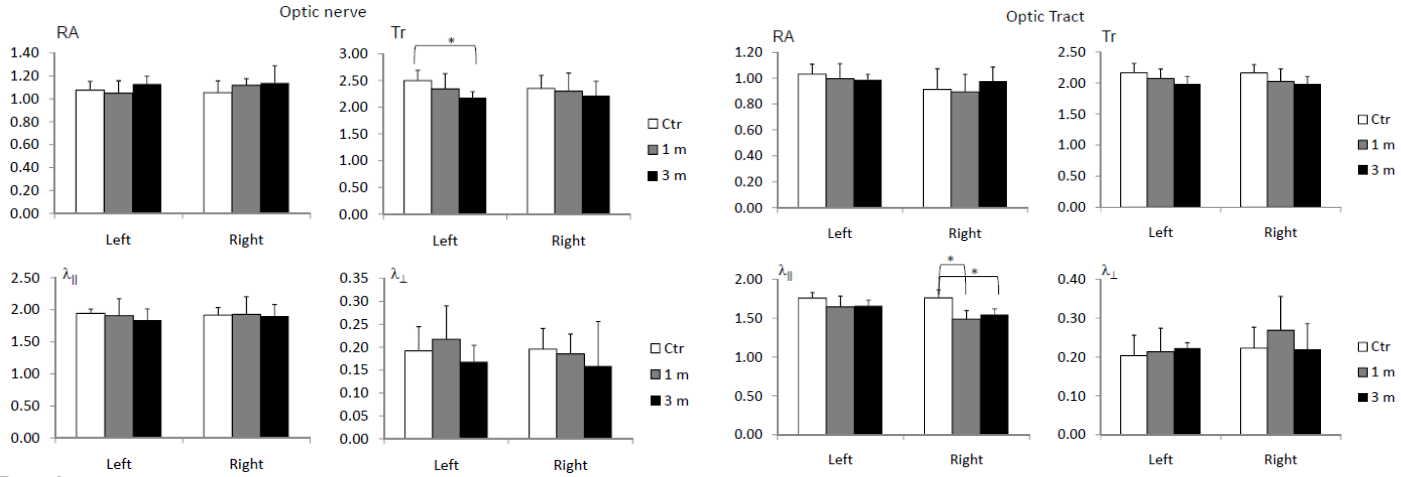
Amyloid Beta (Aβ) is the principal component in amyloid plaques and has been implicated as the primary toxic factor in Alzheimer's disease pathogenesis (1). However, the mechanism of how Aβ to induce neurodegeneration is not clear. Given the fact that a large number of soluble Aβ are produced around synapses (2), despite of the synaptic vulnerability to Aβ, it has never been demonstrated whether a focal exposure of axonal terminals to Aβ may lead to a dying-back axonal degeneration. An experiment designed to allow the axonal terminal sites but not neuronal body (soma) to be exposed to Aβ would provide an answer to this question.

In this study, we address this issue on visual system, in which the optic nerve and optic tract are axons inside the brain, and the soma, the retinal ganglion cells (RGCs), sit in the eye. The Aβ injected into optic tract terminals would be less likely to affected RGC bodies directly. As such, only the axon but not the soma would be affected by Aβ after the brain injection of Aβ. Diffusion Tensor Imaging (DTI) and histology were performed to evaluate the optic tract degeneration after the Aβ injection.

Materials and Methods



Twelve female C57BL/6 mice at 12 weeks old were separated into two groups. For experimental group, Aβ peptides (4 n mole in 3 µl) were injected into the right hemisphere dorsal lateral geniculate (LGd) area, which are the axonal terminals of optic tracts. In 1 and 3 months after Aβ injection, mice were anesthetized with a mixture of oxygen and isoflurane (Baxtor Healthcare Corporation, IL, USA) for imaging. Spin-echo DTI were collected using a Bruker 4.7T BioSpec small animal MRI instrument with TR 3 s, TE 29 ms, diffusion gradient pair (Δ) = 20 ms, diffusion gradient duration (δ) = 3 ms, a six-direction diffusion scheme with b-values of 0 and 0.85 ms/µm^2, slice thickness 0.5 mm, field of view of 1.5 cm x 1.5 cm, and matrix 256 x 256. Using program written in Matlab (MathWorks, Natick, MA, USA), the axial diffusivity ($\lambda_{\parallel}$), radial diffusivity ($\lambda_{\perp}$), relative anisotropy (RA), and trace of the diffusion tensor (Tr) were calculated. Regions of interest (ROI) were selected in optic nerves, optic tracts, corpus callosum, and external capsule. Data were presented as mean ± standard deviation. Repeated measures analysis of variance (ANOVA) was carried out. P-values were considered to be statistically significant at $\alpha < 0.05$.



Results

Among the measured white matter tracts, only optic tracts and optic nerves showed Aβ effects. The ipsilateral optic tracts showed significant a 15% decrease of $\lambda_{\parallel}$. In optic nerves, the only the contralateral but not the ipsilateral optic nerves showed abnormalities. The contralateral optic nerves appeared 10% decreases of Tr in 3 months after Aβ injection.

Discussion and Conclusions

This study demonstrated the axonal degeneration induced by the exposure of axonal terminal sites to the Aβ. After Aβ injection, the ipsilateral optic tracts appeared abnormal with a 15% decrease of $\lambda_{\parallel}$. The significant 10 Tr decrease in contralateral optic nerves may relate to the ipsilateral optic tract degeneration as a result of Aβ injection. All brains were currently under the process for immunohistological examinations.

References (1) Yankner, B. A. et al. Science 245, 417-420, (1989). (2) Cirrito, J. R. et al.. Neuron 48, 913-922, (2005).

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