Synaptic Amyloid Beta Affects Neural Conductivity But May Not Lead to Pre-synaptic Axonal Degeneration

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Introduction

Synaptic deficits and brain atrophy are two major pathological hallmarks in Alzheimer's disease (AD). Synaptic deficits usually occur early in contrast to the neuronal loss which usually occurs late. Thus, it is speculated that the early synaptic deficits may facilitate the later neuronal loss. In AD, the Amyloid Beta (Aβ) is one potent toxin to cause neuropathology (1). Aβ is toxic to neurons and synapses. In this study, we tested the hypothesis that Aβ located in synapses could induce a retrograded axonal degeneration in presynaptic nerves to later cause neuronal loss. To be able to apply Aβ to selectively affect synapses but not the neuronal bodies in vivo, we used the visual system. The advantage of visual system is that the neuronal bodies are retinal ganglion cells (RGCs) locating in the eyes, while the axons are extended to the lateral geniculate nucleus (LGN) in the middle of the brain. Injecting Aβ peptides in LGN would allow Aβ to affect only synapses but not the soma of RGCs.

Materials and Methods

4 nmole or 10 nmole of $A\beta_{1\text{-}42}$ (N = 8 and 5, respectively) was injected in the left LGN of 12-week-old female C57BL/6 mice (2). Longitudinal Diffusion Tensor Imaging (DTI) was collected using a Bruker 4.7T BioSpec with TR 2 s, TE 29 ms, Δ 20 ms, δ 3 ms, 6 gradient directions with b 0.85 ms/μm^2 and 1 b0, NT of 3, Slth 0.5 mm, FOV 1.5 cm x 1.5 cm, and matrix 128 x 128. ROI was selected in optic nerves (ON) and optic tracts (OT). At 3 months after Aβ injection, animals were sacrificed for immunohiostochemistry analysis. For the 10 nmole Aβ treated mice, the visual evoked potentials (VEP) were recorded before sacrificing the animal.

Results

There was no significant change of DTI in Aβ affected nerves compared to controls, regardless of 4 or 10 nmole Aβ injections (Figs. 1 and 2). For the 10n mole Aβ treated mice, we also recorded VEP to examine the visual nervous functions. The Aβ-affected eye showed a significant decrease of VEP amplitude and a significant increase of VEP latency.

Discussion

The synaptic depression caused by Aβ has been acknowledged as one of the key pathological mechanisms to cause the memory loss and cognitive impairment in the early stage of AD (3). It has been speculated that the toxicity of Aβ might not stop at synapses but the consequent cascades may disturb neurons and axons leading to the neuronal loss at a later time point. However, in 3 months after injecting Aβ in LGN, no damage was found in ON and OT. In contrast to the normal-appeared ON and OT, the impaired VEP suggested that the visual functional conduction was affected by Aβ. Aβ may have caused synaptic depression in the RGC terminals. However, the Aβ-facilitated synaptic depression did not lead to pre-synaptic degeneration.

Conclusion

Aβ injected in axonal terminals may impair synapses to adversely affect the neural signal conduction. However, the injured synapses may not lead to a retrograded axonal degeneration to cause a neuronal loss.

References

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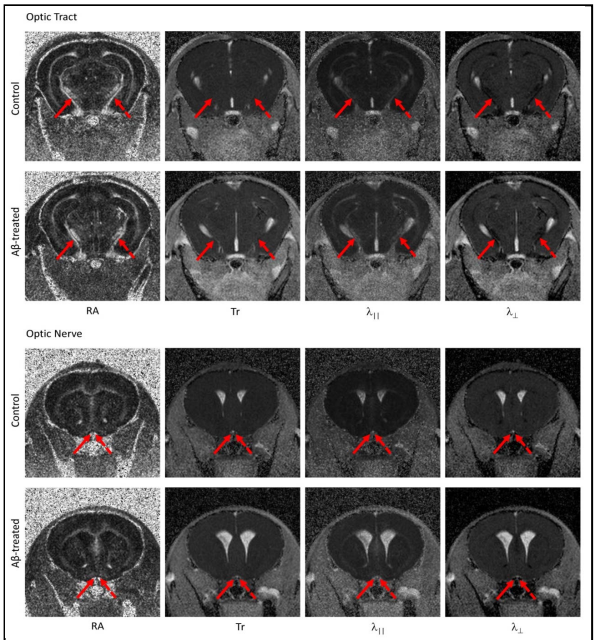

Fig. 1, DTI of Aβ-treated and control mice. The arrows indicated optic nerves and tracts.

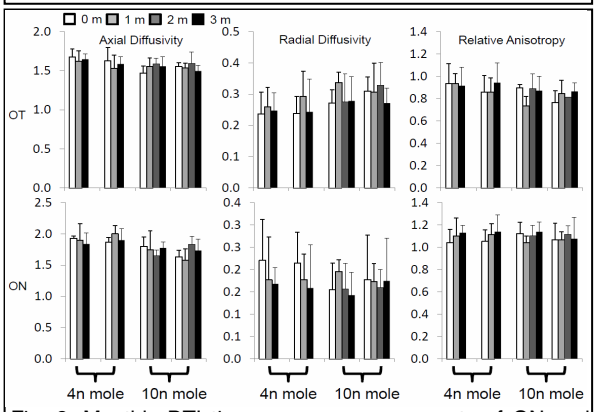

Fig. 2, Monthly DTI time course measurements of ON and OT after 4 n mole or 10 n mole of Aβ injections. There was no significant change caused by Aβ.

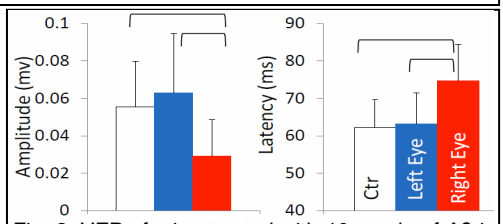

Fig. 3, VEP of mice treated with 10n mole of Aβ in the left LGN. A significant decrease of VEP amplitude and a significant increase of VEP latency was found in the Aβ-affected visual pathway (right eye – left visual cortex) showed.