Early impaired axonal transport in a triple transgenic mouse model of Alzheimer's disease

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Introduction

Alzheimer's disease (AD) is an irreversible neurodegenerative disorder and is the most common cause of dementia among people over 65 years of age. Significant efforts are being made on drug discovery and development to treat symptoms or slow the disease progression. The development of non-invasive neuroimaging methods would be enormously valuable to visualize early, yet subtle, changes in the AD brain, monitor the disease progression, and quantify the effect of drug intervention. Triple transgenic AD (3xTg) mice model harbors $PS1_{M146V}$, APP_{Sw}, and tau_{P301L} and progressively develops both β–amyloid (Aβ) plaques and neurofibrillary tangle (NFT) pathology with accompanying neuronal death in brain regions similar to those seen in human AD [1]. Manganese (Mn^{2+}) can enter excitable cells through voltage-gated calcium channels and can be transported via fast axonal transport mechanism through microtubles in axons toward the projecting neurons. We used manganese-enhanced MRI (MEMRI) to assess the age associated alterations of fast axonal transport rates in 3xTg animals.

Methods

All MR studies were performed at 9.4 T Varian system equipped with a 12 cm gradient coil (40 G/cm, 250 μs) and interfaced to a Varian INOVA console (Varian Inc., CA). A 6-cm diameter Helmholtz volume transmit coil and a 7-mm diameter surface receive coil were used for MR imaging. Three age groups of 3x-Tg mice and age-matched wild type (wt) mice (2 months, n=5; 3 months, n=8; 15 months, n=5 per each genotype) were scanned. Anesthesia was induced by 4% isoflurane mixed with 4 L/min air and 1L/min O_2 and maintained by 1-1.5% isoflurane. Body temperature was maintained at 37˚C using a circulating hot water pad and a temperature controller (Cole-Palmer, NY). Respiration, heart rate, and blood oxygen level were also monitored via respiration pillow and mouse pulse oximeter (SA Instruments, NY; STARR Life Sciences, OH). MR data were acquired before and 1, 6, and 24 h after unilateral and intranasal administration of $MnCl_2$ solution (160 mM, 4 μl) in four separate MRI sessions. Animals were stimulated using amyl acetate for 15 min to enhance uptake of Mn^{2+} in the olfactory neurons. T_1 maps were measured using a modified Look-Locker multislice sequence to acquire multiple phase encodings per inversion pulse (TR/TE = 4/2 ms, FOV = 2 cm, matrix = 128 x 128, thk = 0.5 mm, flip angle = 20°, 22 inversion times, acquisition time = 8.5 min). B_1 maps were measured to correct the effect of flip angle variations in T_1 mapping using a B_1 mapping sequence [2] (TR/TE = 200/3.7 ms, matrix = 128 x 128, nt = 4, thk = 0.5 mm). High resolution T_1-weighted (T_1w) spin-echo data were also acquired (TR/TE = 600/10 ms, nt =2, matrix = 256 x 256, thk = 0.6 mm, scan time = 5 min). T_1 and B_1 maps were generated using software written in IDL (RSI, CO). Bulk axonal transport rates of olfactory neurons were calculated from the time course of R_1 in olfactory bulb (OB). Trans-synaptic axonal transport efficiency was estimated from the $R_1=1/T_1$changes in the olfactory cortex (OC).

Results and Discussion

Figure 1 shows T_1w image (a) and corresponding T_1 map (b) of OB of a 3 month old mouse at 24 h post $MnCl_2$ administration. Unilateral signal enhancement and reduction of T_1 were clearly visible at the right OB. Temporal changes $R_1 = 1/T_1$ in OB of 3 month old mice is shown in Fig. 1c. R_1 in the right OB of 3xTg mice was significantly lower at 6 h and 24 h post $MnCl_2$ administration, indicating impaired bulk axonal transport of in olfactory neurons of 3xTg animals compared with that of age-matched wt animals ($p = 0.05$ for 6 h, $p = 0.003$ for 24 h, n = 8 (wt), n = 5 (3xTg)).

Trans-synaptic transport of Mn^{2+} in olfactory cortex was shown in Fig. 2. Shortening of T_1 in OC was evident from the T1w image (a) and the corresponding T_1 map (b) at 24 h post $MnCl_2$ administration. Figure 2(c) shows comparison of R_1 changes over 24 h in OC at 2, 3 and 15 months old 3xTg and age-matched wt mice. Reduction of R_1 changes was observed in 3 months old mice ($p = 0.01$, n = 8 (wt), n = 5 (3xTg)) and 15 months old ($p = 0.06$, n= 4 each group). Mn^{2+} uptake at the olfactory sensory neurons was estimated from the signal enhancement at the turbinate areas (arrow in Fig. 1(a)). No significant difference of signal enhancement in turbinate between 3xTg and wt mice was found in all three age groups. Based on the similar uptake of Mn^{2+} at the olfactory neurons, the lower Mn^{2+} concentration in OB and OC of 3xTg mice can be interpreted as the lowered axonal transport rates in olfactory sensory neurons and projecting neurons from OB to OC. The observation of slower axonal transport in 3xTg mice compared with that in age-matched wt mice as early as 3 months of age suggests the impairment of axonal transport is an early event in AD pathology preceding deposition of Aβ plaques and neurofibrillary tangles. It is also consistent with the previous observation of lowered axonal transport rates in a different transgenic model of AD (tg2576) prior to Aβ plaque deposition [3].

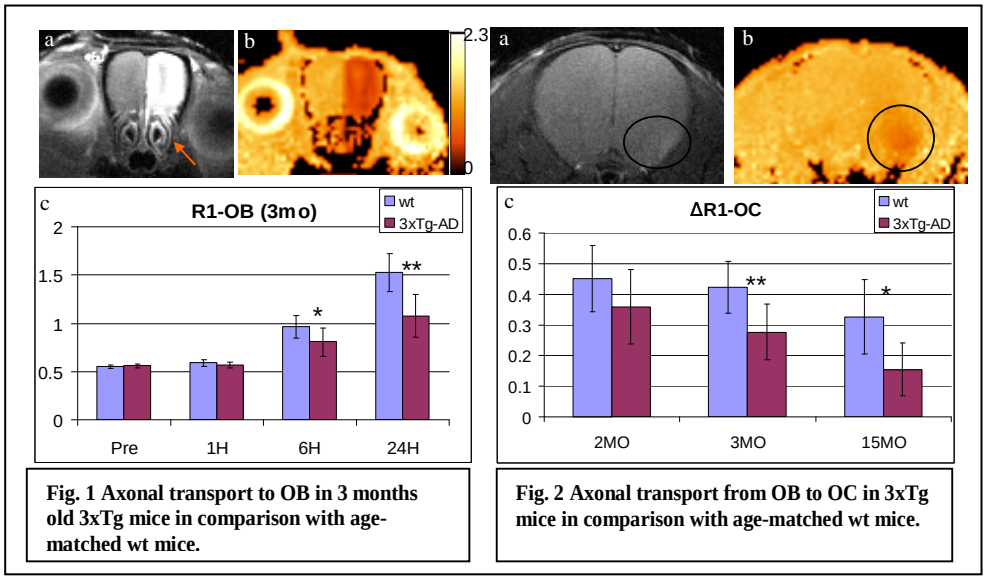

Fig. 1 Axonal transport to OB in 3 months old 3xTg mice in comparison with age-matched wt mice.

Fig. 2 Axonal transport from OB to OC in 3xTg mice in comparison with age-matched wt mice.

References

[1] Oddo et al. Neuron 39:409-421 (2003) [2] Pan et al, MRM 40:363-369 (1998) [3] Smith et al. NeuroImage 35:1401-1408 (2007), Supported by a grant from Alzheimer's association.