Quantification of Microtubule Stabilizing Drug Treatment effect on Axonal Transport Rate in a Transgenic Mouse Model of Alzheimers Disease

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Introduction

Quantitative assessment of the treatment efficacy is crucial in pre-clinical trials to facilitate the finding of novel drugs for delaying and even possibly curing the disease. We have recently reported a novel non-invasive method to quantify axonal transport rates in animal models of Alzheimer's disease (AD) [1]. In this study, we aimed to evaluate the efficacy of recently identified agents for AD treatment, TH237-A, in the brains of the triple transgenic mouse model of AD (3xTg-AD), which 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 [2]. TH237-A is known to be effective in protecting neurons against Aβ toxicity, and decreasing the abnormal tau phosphorylation by stabilizing microtubules (MT) in cultured neurons. In addition, TH237-A can permeate the blood-brain barrier [3]. The 3xTg-AD mice were treated with TH237-A and a vehicle (Captisol) for one year and axonal transport deficit were measured using manganese-enhanced MRI (MEMRI) at 9.4T.

Methods

Three groups of 3xTg-AD mice (TH237-A: n = 4, vehicle: n = 4, no treatment: n = 3) and age-matched wild type (wt) mice (TH237-A: n = 4, vehicle: n = 4) were scanned before drug treatments at the age of 3 months (Pre) and following 12 months of drug treatments (P12MO at 15MO old). All MR studies were performed using a 9.4 T Varian system equipped with a 12 cm gradient insert (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. 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 was monitored via a respiration pillow (SA Instruments, NY). MR data were acquired prior to intranasal administration of $MnCl_2$ solution and 1, 6, and 24 h after (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 [4] (TR/TE = 200/3.7 ms, matrix = 128 x 128, nt = 4, thk = 0.5 mm). 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 rate of R_1 changes in an olfactory bulb (OB) between 1 h and 6 h after $MnCl_2$ administration.

Results and Discussion

Figure 1 shows T_1 maps of OBs at Pre, P12MO treatment, and age-matching 15MO old 3xTg-AD without treatment. Figure 2 shows group comparison of R_1 values between 3xTg-AD and wt. The R_1 value of the 3xTg-AD mice was significantly lower at 6 h post $MnCl_2$ administration, indicating impaired bulk axonal transport in the olfactory neurons of 3xTg-AD compared with that of wt (p = 0.02, n = 8 for wt, n = 4 for 3xTg-AD) at 3MO of age [1]. Furthermore, 3xTg-AD showed age-dependent axonal transport deficit at 15MO old (30% reduction, p=0.009) without any treatment. Post treatment MEMRI showed a 38% reduction in axonal transport rates for wt from Pre to P12MO treatments (p=0.001), whereas a 3% increase for 3xTg-AD was measured overall, which is within the error range.

Compared to the non-treated mice, the TH237-A treated mice showed no decrease in axonal transport rates in 3xTg-AD. Our preliminary data indicate that TH237-A may be effective in preserving axonal transport integrity in 3xTg-AD mice. However, we also note that the mice treated with the vehicle (Captisol) alone showed similar preservation of axonal transport rates following P12MO treatments to those of the TH237-A treated mice (date not shown). Thus, the effect of the vehicle treatment on axonal transport in 3xTg-AD mice may require further study.
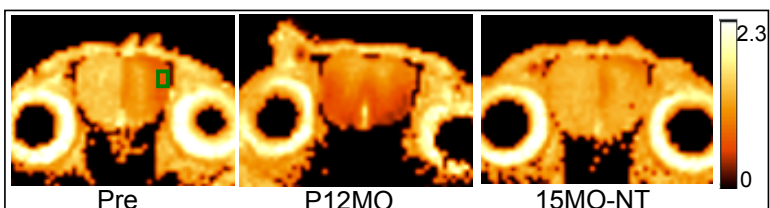

Fig 1. T_1 map of 3xTg-AD at Pre, Post-12MO, and 15MO non-treated (NT) mice. All images are acquired at 6 h post $MnCl_2$ administration and small green rectangle indicates an ROI in which R_1 is measured.
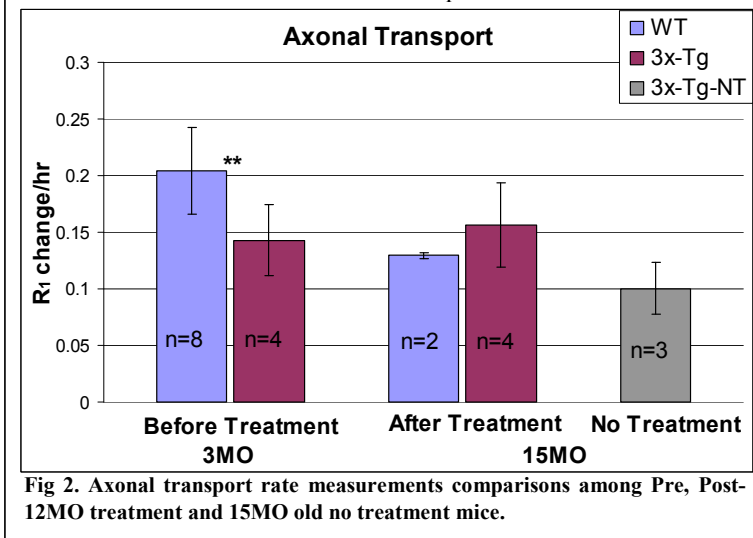

Fig 2. Axonal transport rate measurements comparisons among Pre, Post-12MO treatment and 15MO old no treatment mice.

References

[1] Kim et al, *ISMRM09* Abstract #540 [2] Oddo et al., *Neuron* 39:409-421 (2003) [3] Michaelis et al., *Current Alzheimer Research* 3 :215-219 (2006) [4] Pan et al., *MRM* 40:363-369 (1998).