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 Alzheimers 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 PS1M146V, APPSw, and tauP301L and progressively develops both ß-amyloid (Aß) 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 Aß 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 O2 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 MnCl2 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 Mn2+ in the olfactory neurons.

T1 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). B1 maps were measured to correct the effect of flip angle variations in T1 mapping using a B1 mapping sequence [4] (TR/TE = 200/3.7 ms, matrix = 128 x 128, nt = 4, thk = 0.5 mm). T1 and B1 maps were generated using software written in IDL (RSI, CO). Bulk axonal transport rates of olfactory neurons were calculated from the rate of R1 changes in an olfactory bulb (OB) between 1 h and 6 h after MnCl2 administration.

Results and Discussion
Figure 1 shows T1 maps of OBs at Pre, P12MO treatment, and age-matching 15MO old 3xTg-AD without treatment. Figure 2 shows group comparison of R1 values between 3xTg-AD and wt. The R1 value of the 3xTg-AD mice was significantly lower at 6 h post MnCl2 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.

References

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