Mitochondrial Catalase Overexpression recovers axonal transport deficits and improves hippocampal long-term potentiation in APP/PS1 mice

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Background: Alzheimer's disease (AD) is a progressive, neurodegenerative disease that is currently the 6th leading cause of death in the United States. Although its pathological hallmarks of amyloid plaques and neurofibrillary tangles have been well characterized, targeted therapies have been met with limited success in clinical trials. Recent studies have suggested that microtubule-based axonal transport deficits can be detected *in* vivo in AD models prior to the onset of either plaques or tangles. In addition, evidence of redox imbalance has been shown in both patient samples and *in vivo* in mouse models of the disease, however clinical trials have been met with limited success, perhaps due to lack of specificity. Previous studies have also displayed a correlation between increases in oxidative stress and axonal transport deficits. Crossing superoxide dismutase (SOD2) overexpressing mice with an amyloid model of AD resulted in improvements in axonal transport, learning and memory, and amyloid pathology, indicating that superoxide is a key player in the pathogenesis of AD. In this study, we sought to determine if hydrogen peroxide also plays a role in AD pathology by crossing mice overexpressing mitochondrial catalase (MCAT) to the APP/PS1 mouse model of AD. *We hypothesized that APP/MCAT mice will show improvements in axonal transport accompanied by long-term potentiation.*

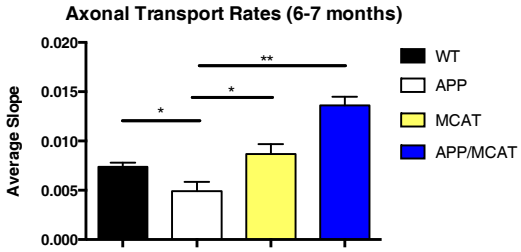

Figure 1: Axonal transport rates are represented by average slope calculation. Data were analyzed by One Way ANOVA with Multiple Comparisons.

Methods: APP/PS1 mice were crossed to MCAT mice and four groups were used throughout the course of this study (WT, APP, MCAT, and APP/MCAT). Measurements for axonal transport were conducted using the MEMRI protocol as previously described. All animals were handled in compliance with institutional and national regulations and policies.

Imaging Protocol: All images were obtained using a 9.4T, Bruker Avance BioSpec Spectrometer with a 21cm horizontal bore (Bruker BioSpin, Billerica, MA) and a 35mm resonator. Mice were anesthetized using 5% isoflurane with oxygen and placed into the animal holder, where they were kept at 2% isoflurane for the rest of the imaging time. Mice were imaged using a Manganese Enhanced MRI (MEMRI) protocol to obtain T_1-weighted images. Imaging parameters used for MEMRI: TE=8.5 ms, TR=504 ms, FOV=3 cm, matrix size=128x128, taking 32 min, 15 seconds. Paravision 4.0 software (Bruker BioSpin, Billerica, MA). During imaging, body temperature was maintained at 37.0°C using an animal heating system (SA Instruments, Stony Brook, NY).

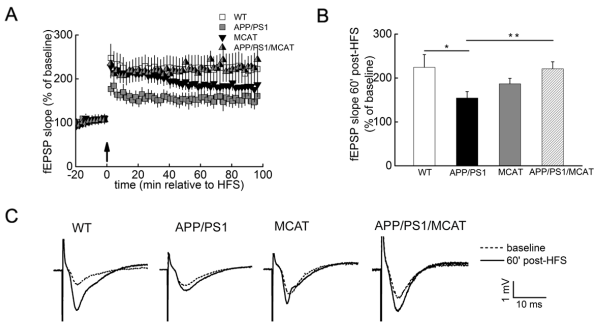

Figure 2: Hippocampal LTP deficits in APP/PS1 mice are prevented by overexpressing catalase. *A,* HFS-induced hippocampal LTP was inhibited in APP/PS1 mice (gray squares, n=8) compared to LTP in WT mice (open squares, n=8). In contrast, hippocampal LTP was sustained in APP/MCAT mice (half-filled triangles, n=9). *B,* Cumulative data showing mean fEPSP slopes 60 min post-HFS from the LTP experiments in panel *A*. Data were presented as mean +SEM. Unpaired independent *t*-test. **p*<0.05, ***p*<0.01. *C,* Representative fEPSP traces before and after HFS for LTP experiments shown in panel *A* and *B*.

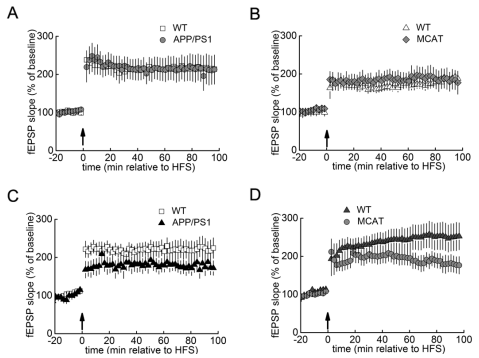

Figure 3: ***A,*** HFS-induced hippocampal LTP is comparable in 3 months old APP/PS1 mice (gray circles, n=11) and WT littermates (open squares, n=11). ***B,*** Similar hippocampal LTP is induced in 3 month old MCAT mice (gray diamonds, n=9) and WT littermates (open triangles, n=12). ***C,*** HFS-induced hippocampal LTP is inhibited in 6 months old APP/PS1 mice (black triangles, n=6), compared to WT littermates (open squares, n=16). ***D,*** HFS-induced hippocampal LTP is inhibited in 6 months old MCAT mice (gray circles, n=7), compared to WT littermates (dark gray triangles, n=6).

Data Analysis: Obtained images were analyzed using Paravision 4.0 software. A region of interest (ROI) within the olfactory bulb was selected. T_1-signal intensity (SI) and times within these ROIs were measured and normalized to SI measured from a water phantom. Graphs and statistics from all data were generated using Prism (GraphPad Software, San Diego, CA).

Results: Upon evaluating APP/MCAT mice at 6-7 months of age, we measured significant improvements in axonal transport rate (Fig. 1) and long-term potentiation (Figs 2 & 3) in APP/MCAT mice when compared to APP mice.

Discussion: We have completed a genetic study that investigated the effects of mitochondrial catalase on amyloid pathology in the APP/PS1 mouse model of AD. We demonstrate axonal transport measurement as an early indicator of improvements in this mouse model and further elucidate the role of hydrogen peroxide as a key contributor to microtubule based axonal transport. Our current study lays the foundation for future studies of oxidative stress and specific contributors to the pathogenesis of AD.

References: (1) Inoue, et al. *Rev. Neurosci.* 2011; 22(6):675-94. **(2)** Massaad, et al. *PLOS One*, 2010. **(3)** Smith, et al. *Neuroimage.* 2007; 35(4): 1401-1408. **(4)** Massaad, et al. PNAS 2009.