

Imaging biophysics of axonal transport with MEMRI: Optic tract transport is altered in mouse model of Alzheimer's disease

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Introduction

Recent evidence implicates transport defects in neurodegeneration, epilepsy, and glaucoma. The oriented neuronal projections from the retinal ganglion cells in the optic tract proved an excellent system in which to detect the effects of genetics or disease on axonal transport. Manganese-enhanced MRI (MEMRI) allows tracing of neuronal tracts in the optic tract of living animals, which thus offers the potential to measure the dynamics of axonal transport over time in genetically controlled animals (1, 2). We previously reported in time-lapse MRI of intensity changes along the optic tract that Mn⁺⁺ transports more slowly in the optic tract of mice with a genetic knock-out of the kinesin light chain gene (3). Conventional kinesin is the cellular motor thought to mediate a portion of axonal transport. This result demonstrated that MEMR imaging is sensitive enough to detect transport differences between genetically distinct mice. Here we report the effect of genetic manipulation of amyloid precursor protein (APP) on Mn⁺⁺ transport by time-lapse T1-weighted slab images acquired at 6 min intervals over the course of 3.0 hr after injection of Mn⁺⁺ into the posterior chamber of the eye. We tested 16 mo old mice expressing a human APP mutant protein known to cause Alzheimer's disease (SwAPP) and their wildtype littermates (TTA)(4). At this age, this mutant mouse strain has Alzheimer's-type plaques in the brain.

Materials and Methods

MnCl₂ (200 mM) was injected into the vitreous of the right eye (0.25 μ l). MR images of the living mouse were acquired at 11.7T (Bruker BioSpin MRI Inc.) using a 20mm RF birdcage coil. Slab images of the optic tract (0.45cm thick slab with 32 slices) at 6-minute intervals for 3 hours beginning 30 minutes post injection with a 3D RARE sequence (TR/TE 300/5 ms, 4 echoes, 1 averages, FOV 1.5²x0.45 cm, and 128²x32 matrix size). At 24 h after MnCl₂ injection a slab image was captured with the same protocol as the time lapse images. In addition, a whole brain image was acquired with a T₁ weighted 3D UFLARE sequence (TR/TE 300/5 ms, 4 echoes, 2 averages, FOV 2.2x1.5² cm, and 256x128² matrix size).

Fig. 1: MR Time-lapse of optic tract transport

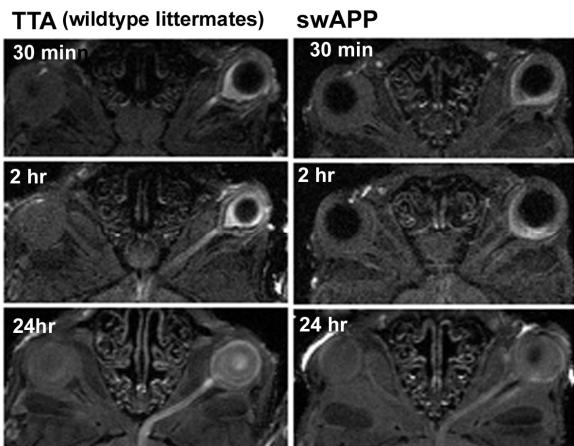
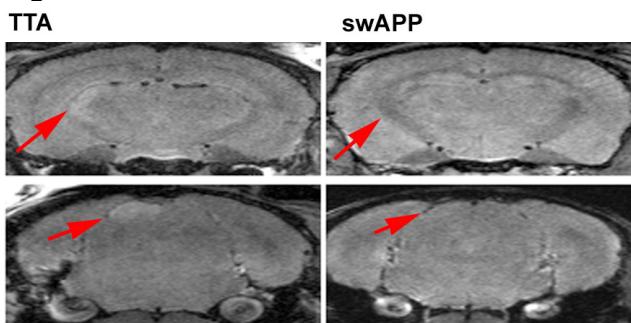


Fig. 2: Accumulation of Mn⁺⁺ at 24



underlying factor in neurodegeneration.

Results and Discussion

Mn⁺⁺ enhanced intensity spread from the right eye along the optic tract in wildtype animals between 30 min and 2 hr, reaching the optic chiasm by the later time point, a distance of 5-6 mm consistent with fast axonal transport rates (average velocity of 1 μ m/s) (Figure 1). At 30 min, the earliest time point, Mn⁺⁺-induced intensity changes were obvious in the globe of the eye and at the entry into the optic tract. At a later time point, 2 hr, Mn⁺⁺-induced intensity progressed further along the tract in the age-matched wildtype than in the 16 mo old swAPP mouse. By 24 hr, the optic tracts in both mice were highlighted, although the swAPP had less signal. Mn⁺⁺-accumulations in the lateral geniculate (Figure 2, top panels) and in superior colliculus (Figure 2, lower panels) at 24 hr of these same two mice paralleled the differential transport, with barely discernible increased intensity in the swAPP compared to robust signal in wildtype/TTA.

Conclusion

After Mn⁺⁺ injection into the eye, visually detectable increases in intensity occurred gradually along the optic tract. The rate that intensity increases can be monitored by capturing MR images at regular time intervals. Minor delays in transport not detectable at later time points (24 hr), are revealed in time lapse sequences captured early in the transport process. Quantitative analysis of intensity changes along the optic tract in time lapse series will therefore lead to more detailed interpretations of the transport properties in these and other genetic variants of living mice. This study shows that increased expression of APP is correlated with decreased transport and accumulation of Mn⁺⁺ at distant points along a neuronal pathway in aging mice (16 mo) when plaque formation has occurred(4). Thus transport dynamics as well as accumulation are useful indicators of neural function. These data also support conclusions from previous studies implicating transport as an

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