Axonal conduction velocity in CA1 area of hippocampus is reduced in a mouse model of Alzheimer's disease, rTg4510

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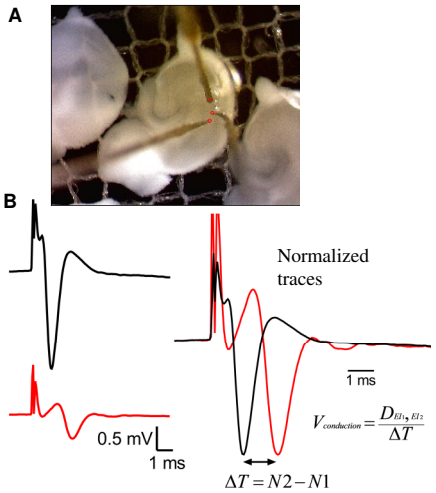
Background

We previously reported that conduction velocity of Schaffer collaterals in CA1 area of hippocampus is reduced in an age-dependent manner in two amyloid precursor protein transgenic mouse models, line 41 (APP Swe/Lon) and APP/PS1 (cross between tg-2576 (APPSwe) and a mutant PS1 (m146L) mouse). Here we asked whether similar deficit in V_C is also present in a mouse model of tauopathy, rTg4510, which over-expresses microtubule-associated protein tau carrying a P301L mutation. Hyper-phosphorylated tau disrupts axonal cytoskeleton and transport, potentially resulting in abnormal levels of Na^+ and/or K^+ channels and Na^+/K^+ – ATPases, which may contribute to changes in V_C.

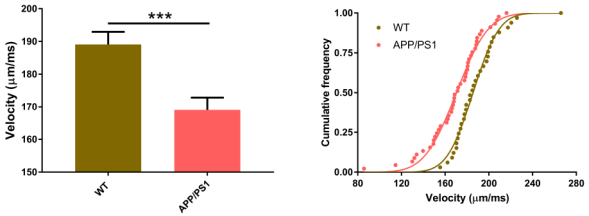
Methods

We measured V_c in axons of Schaffer collaterals in CA1 area of hippocampus. We used a transverse hippocampal slice preparation with two extracellular recording electrodes to capture propagation of compound action potentials (CAPs) elicited by a stimulating electrode in the presence of synaptic transmission blockers (CNQX, APV, and picrotoxin). V_c (in µm/ms) was calculated as d/t, where d is the linear distance between recording electrodes (200µm-600µm) and t is the time of CAP propagation. The distance between recording electrodes and the width of a stimulating electrode were determined using two separate deep learning neural networks trained to detect the width of calibration probe (stim electrode) and tips of recording probes.



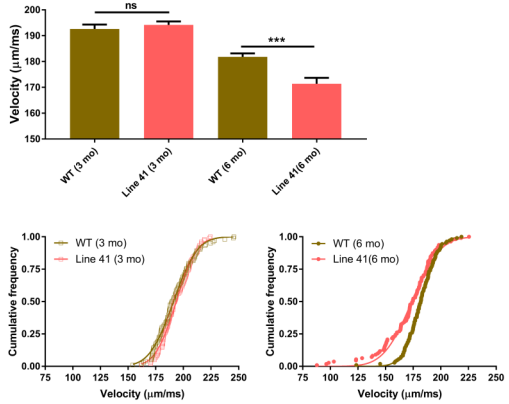
***A**. An image of a hippocampal slice showing placement of stimulating and recording electrodes in the stratum radiatum layer of CA1. **B**. Representative recordings from electrode 1 and 2.*

Axonal conduction velocity is reduced in 24 mo old APP/PS1



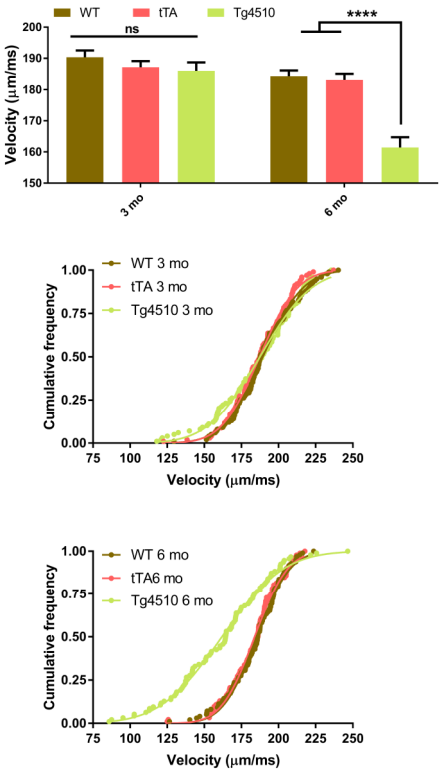
***Left panel**. Schaffer collateral conduction velocity is lower in **24 mo old** APP/PS1 compared to WT controls (WT n= 3 mice, 33 slices; APP/PS1 n= 4 mice, 45 slices; t-test, p < 0.0004). **Right panel**. Cumulative frequency distribution of conduction velocities is shifted to the smaller values in APP/PS1 (cumulative Gaussian fits are statistically different, p < 0.0001).*

Reduction in axonal conduction velocity is age-dependent in Line 41



***Top panel.** Only 6 mo and not 3 mo old Line 41 mice show a reduction in conduction velocity compared to age-matched controls (3 mo WT n= 5 mice, 103 slices; Line 41 n= 5 mice, 103 slices; 6 mo WT = 5 mice, 108 slices; Line 41 = 5 mice, 111 slices. Two-way ANOVA, genotype: F(1,421) = 6.4, p=0.012; age: F(1,421) = 92.3, p<0.0001; interaction: F(1,421) = 11.8, p=0.0007 ; Tukey's multiple comparisons test, p=0.0001).*
***Lower panel.** Cumulative frequency distribution of conduction velocities for 6 mo and not 3 mo old Line 41 is shifted to the lower values (cumulative Gaussian fits are statistically different, p < 0.0001).*

Reduction in axonal conduction velocity is age-dependent in rTg4510



***Top panel.** Only 6 mo and not 3 mo old Tg4510 mice show a reduction in conduction velocity compared to age-matched controls (3 mo WT n=5 mice, 99 slices; tTA n=5 mice, 102 slices; Tg4510 n=5 mice, 99 slices; 6 mo WT = 5 mice, 98 slices; tTA n=5 mice, 92 slices; Tg4510 n=5 mice, 94 slices. Two-way ANOVA, genotype: F(2,578)=19.15, p<0.0001; age: F(2,578) = 36.05, p<0.0001; interaction: F(2,578) = 11.37, p=0.0001; Tukey's multiple comparisons test, p<0.0001).*
***Middle and Lower panel.** Cumulative frequency distribution of conduction velocities for 6 mo and not 3 mo old Tg4510 is shifted to the lower values (cumulative Gaussian fits are statistically different, p < 0.0001).*

Associational and commissural fibers

- CA3 pyramidal cells give rise to associational and commisural pathways in addition to Schaffer collaterals (Paxinos, 1995)
- CA3 and CA2 pyramidal cells project to all portions of the hippocampus (Ishizuka et al., 1990; Amaral and Witter, Ch. 21 in Rat Nervous System, Ed. Paxinos G.)
- Axonal arborizations of single CA3 and CA2 cells project to as much as 75% of the septo-temporal extent of the ipsi- and contra-lateral CA1 fields (Tamamaki et al., 1984, 1988)
- **If one speculates that both associational and commissural fibers in AD models also exhibit slowing of AP propagation, the distances that these fibers span are even greater, which could result in even larger time delays in AD mouse models.**

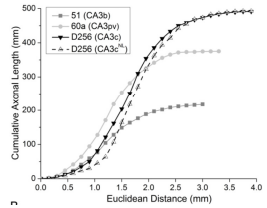


Figure 3 from Ropirredy et al 2011 showing cumulative axon length vs. Euclidean distance

Summary

- We find that conduction velocity in three AD mouse models is reduced compared with age-matched WT controls
- Reduction in conduction velocity is greatest in rTg4510, a mouse model of tauopathy
- Reduction in conduction velocity may result in temporal dysregulation of hippocampal networks, affecting memory and cognition

References

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