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Is there a compensatory mechanism restoring synaptic plasticity in aging tau transgenic mice?

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Introduction

The intracellular accumulation of hyperphosphorylated tau protein characterizes many neurodegenerative diseases such as Alzheimer's disease and frontotemporal dementia. A critical role for tau is supported by studies in transgenic mouse models expressing the P301L mutation with accumulation of mislocated, hyperphosphorylated human tau in hippocampal pyramidal neurons of old as well as young mice[1]. Especially the somatodendritic mislocalization of hyperphosphorylated tau seems to affect the memory-forming neuronal network of the hippocampus. To show the consequences of soluble mislocated hyperphosphorylated tau within neurons of aged (13-24months) and young (5-10weeks) mice, the hippocampal network was analyzed by field potential measurements.

Methods

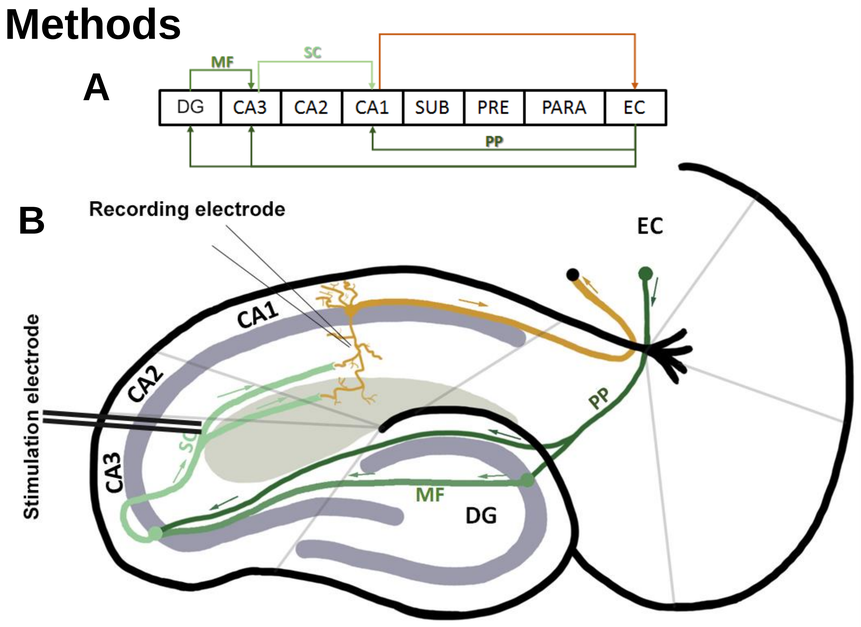


Figure 1: Hippocampal connectivity and electrode location: (A) Schematic illustration of the hippocampal connectivity. (B) Illustration of electrode location in the hippocampal network. CA, cornu Ammonis; DG, dentate gyrus; EC, entorhinal cortex; SUB, subiculum; PRE, presubiculum; PARA, parasubiculum; PP, performant path; MF, mossy fibers; SC, Schaffer collaterals (fecit Leander E. Huggenberger).

- Extracellular field potential recordings were performed in acute brain slices from P301L tau transgenic pR5 mice at the age of 19-22 months and 5-10 weeks old pR5 mice.
- Response to stimulation of the Schaffer collaterals were analyzed using a current-clamp mode of HEKA amplifier.

Result 1: Long- term potentiation (see also Poster 335)

The comparison between old and young non-tg mice revealed no differences but both are significantly different to all tg mice. Moreover, the comparison between old and young tg pR5 mice showed significant differences in peak fEPSP amplitudes over the whole time window after HFS (**p<0.01; old tg pR5 151.8±3.4% and young tg pR5 119.8±3.8%). Furthermore, young and old tg pR5 mice show significant differences in the time window from 10 to 55min after HFS of 121.4±3.7% (young tg pR5 mice) to 153.4±2.0% (old tg pR5 mice; **p<0.01; Figure 2)

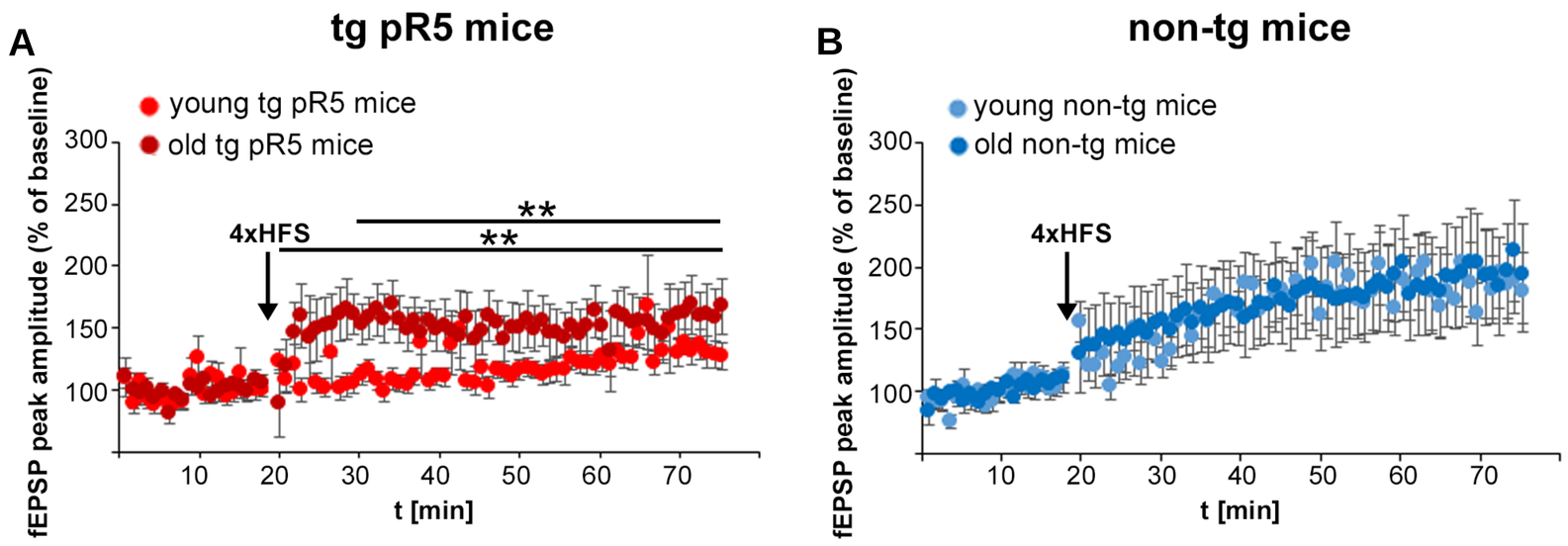


Figure 2: Impaired hippocampal synaptic plasticity in young and old tg pR5 mice: (A) Comparison between LTP induction between old and young tg pR5 mice revealed a significant reduction in fEPSP amplitude in the time window from 0-55min after HFS: old tg pR5 mice 151.8% ±3.4% and young tg pR5 mice 119.8% ±3.8% (p<0.002) and from 10-55min after HFS: old tg pR5 mice 153.4 ±2.0% and young tg pR5 mice 121.4% ±3.7% (p<0.002). (B) Comparison between old and young non-tg mice revealed no significant differences. (Average over 18 minutes prior to HFS set to 100%, all data are shown as mean SEM, **p<0.01, Mann-Whitney U-test).

Result 2: Paired pulse stimulation

The comparison between the two age groups revealed no differences in PPR obtained from old and young non-tg mice but highly significant differences between old and young tg pR5 mice at all interpulse intervals and a change from PPD in young mice to PPF in old mice (Figure 3)

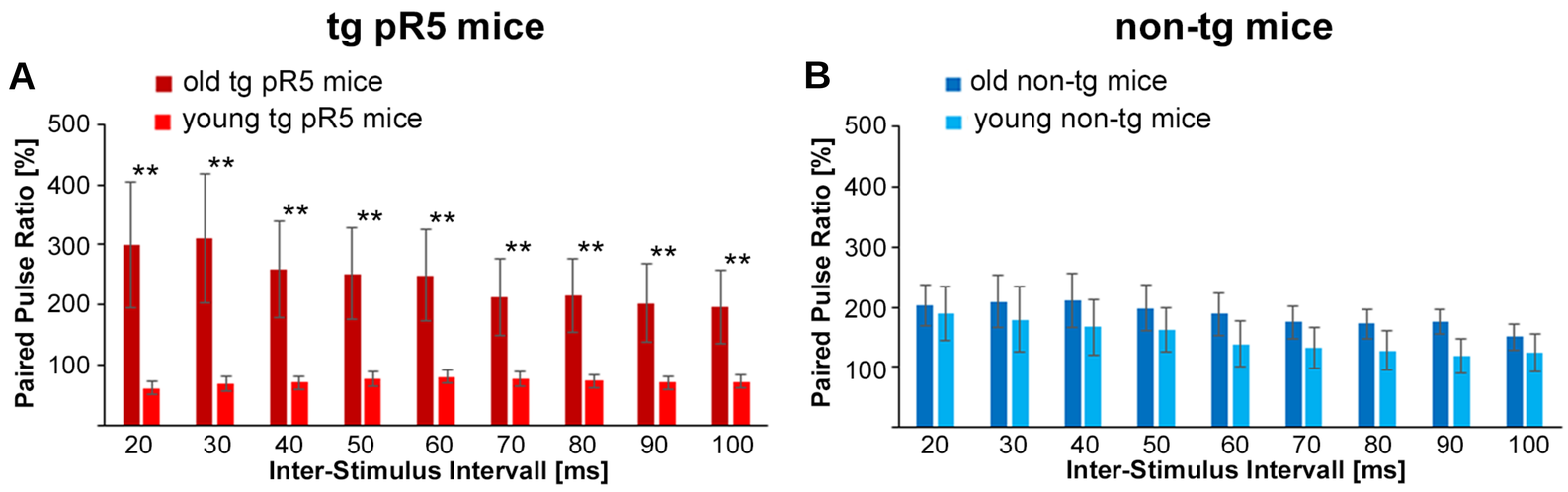
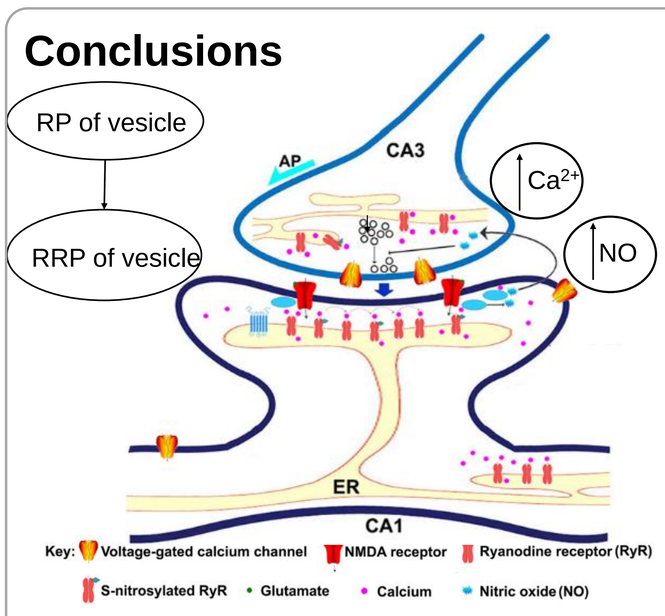


Figure 3: Impaired hippocampal synaptic plasticity in young and old tg pR5 mice: (A) Comparison between old and young tg pR5 mice revealed a significant reduction in PPR at all measured ISIs (ISIs: 20ms p< 0.003; 30ms p<0.003; 40ms p<0.003; 50ms p<0.004; 60ms p<0.004; 70ms p< 0.007; 80ms p< 0.004; 90ms p< 0.009; 100ms p< 0.008). (C) The PPR of both non-tg age groups show no significant differences at all ISIs. PPF indexes were calculated as mean paired pulse ratio (fEPSP peak amplitude of 2nd/1st amplitude) all data are shown as mean SEM (**p<0.01, t-test)

Conclusions



Possible compensatory mechanisms

1. Upregulation of nitric oxide concentration[2] (Figure 4)
   - Increases ryanodine receptor (RyR) opening probability
   - Converts of the reversed pool (RP) of vesicle into a readily releasable pool (RRP) of vesicle
   - Increases insertion of NMDAR and AMPAR
2. Elongation of the Axon initial segment (AIS)[3]
3. Adult hippocampal neurogenesis[4]
4. Increase in mushroom spine volume[5]

(see also Poster 349)

Figure 4: Illustration of possible compensatory mechanism
Upregulation of nitric oxide (NO) within the post and presynapse restores synaptic plasticity in senescent pR5 mice. Modified after Chakroborty et al. 2015

References

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