Differences in synaptic dysfunction between rTg4510 and APP/PS1 mouse models of Alzheimer's disease

Simon Gelman, Jonathan Palma, Patricia Kabitzke, Geoffrey Tombaugh, Afshin Ghavami

PsychoGenics Inc, Montvale, NJ, USA

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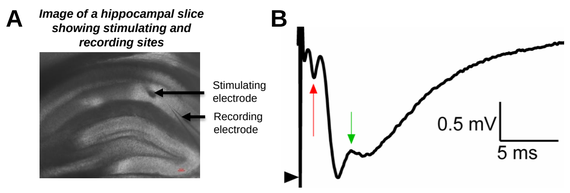
Background

Neurofibrillary tangles with accelerated amyloidosis and plaque formation are widely thought to play major roles in the development of Alzheimer's disease (AD) pathology. The rTg4510 mouse, a model of tauopathy, overexpresses P301L mutant human Tau in the forebrain (SantaCruz et al, 2005; Kopeikina et al, 2013; Ramsden et al, 2005). The APP/PS1 transgenic mouse overexpresses mutated forms of the genes for human amyloid precursor protein (APPsw) and presenilin 1 (m146L) and is used to study amyloid deposition (Holcomb et al, 1998). Generally, these lines of mice exhibit an age-dependent and region-specific progression of neuropathology (Polydoro et al, 2009; Dalby et al, 2014; Trinchese et al, 2004). Additionally, synaptic dysfunction is evident in early development of pathology. However, there is no consensus about the extent to which **basal synaptic transmission (BST)** and synaptic plasticity are affected in these models (Polydoro et al, 2009; Dalby et al, 2014; Trinchese et al, 2004).

Here we examined basal synaptic transmission, short and long-term synaptic plasticity at the Schaffer collateral-CA1 pyramidal cell synapses in APP/PS1 and rTg4510 transgenic mouse models of Alzheimer's disease.

Methods

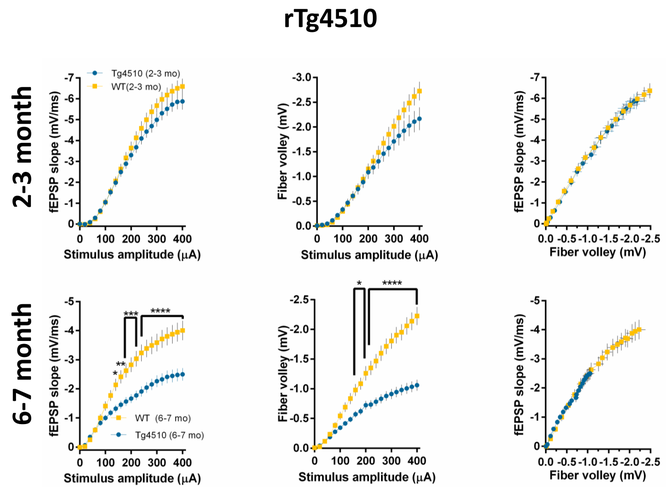
We used extracellular field potential recordings to study BST, short-term plasticity (PTP, post-tetanic potentiation; PPF, paired-pulse facilitation) and long-term potentiation (LTP) at the Schaffer collateral-CA1 pyramidal cell synapses in young and old rTg4510 (2-3 and 6-7 month old) and young and old APP/PS1 mice (2-3 and 8-10 month old). **Statistics**: Data are presented as mean±SEM. T-test or 2-way ANOVA; Sidak's multiple comparisons test (** p<0.01, *** p<0.001, **** p<0.0001).



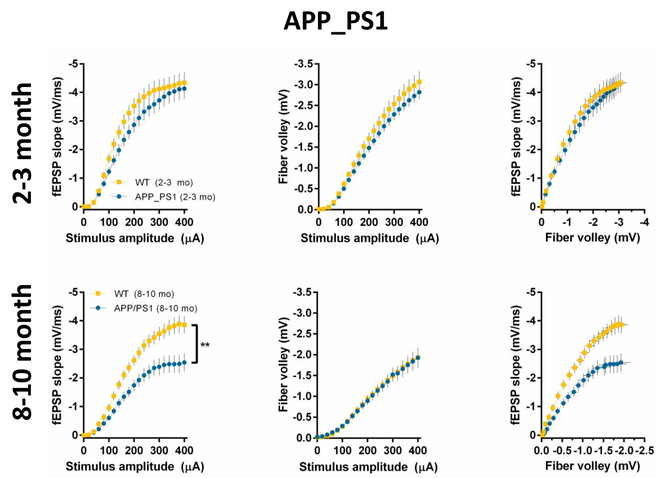
A. *An image of a hippocampal slice showing placement of stimulating and recordings electrodes positioned in the stratum radiatum layer of CA1.* ***B***. *A representative recording.* ***Black arrow*** *- stimulus artifact,* ***red arrow*** *-* ***a pre-synaptic fiber volley (FV)****, which reflects the summed action potentials of local axons. FV is followed by a field excitatory post-synaptic potential (fEPSP).* ***Green arrow*** *- a population spike generated in the pyramidal cell layer in response to synaptic activation.*

Results

Basal Synaptic Transmission

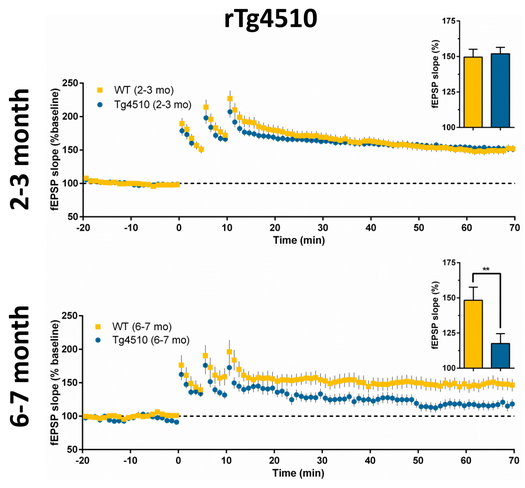


Top panel*. No changes in fEPSP slope or FV amplitude were observed in 3 mo old mice (WT n=60; rTg4510 n=51 slices).* ***Lower panel****. Six month old rTg4510 mice exhibit smaller fEPSP slope and fiber volley when plotted against stimulus amplitude.* ***No deficit in BST is observed when fEPSP slope is plotted against FV*** *(WT n=49; rTg4510 n=50 slices).*

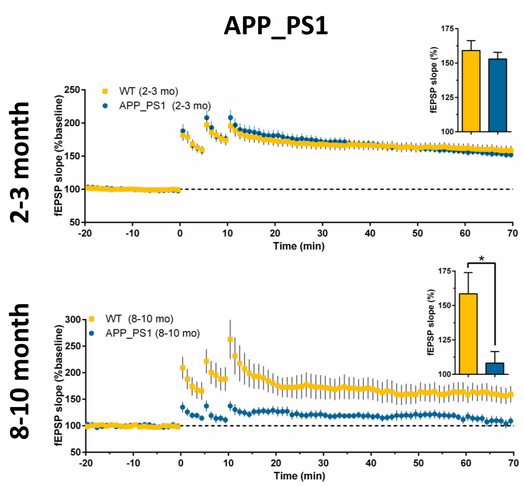


Top panel. *No changes in fEPSP slope or FV amplitude were observed in 3 mo old mice (WT n=32; APP/PS1 n=31 slices).* ***Lower panel.*** *8-10 mo old APP/PS1 mice exhibit smaller fEPSP slope, but unaffected FV amplitude when plotted against stimulus amplitude.* ***A deficit in BST is observed when fEPSP slope is plotted against FV*** *(WT n=42; APP/PS1 n=36 slices).*

LTP

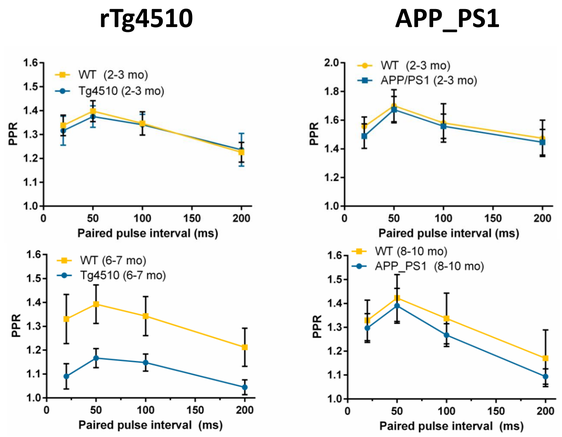


Time-course of normalized fEPSP slope.
Top panel. *3 mo old rTg4510 – no LTP deficit (WT n =29; rTg4510 n=29 slices).* ***Lower panel.*** *8-10 mo old exhibit LTP deficit (WT n =18; rTg4510 n=13 slices).* ***Insets:*** *Summary of data taken from the last 5 minutes of recordings.*



Time-course of normalized fEPSP slope.
Top panel. *3 mo old APP/PS1 – no LTP deficit (WT n =32; APP/PS1 n=30 slices).* ***Lower panel.*** *8-10 mo old exhibit LTP deficit (WT n =12; APP/PS1 n=11 slices).* ***Insets:*** *Summary of data taken from the last 5 minutes of recordings.*

Paired Pulse Facilitation



Left panel. *PPR is reduced in 6 mo old rTg4510 (WT n =17; rTg4510 n=17 slices).* ***Right panel.*** *PPR is unchanged in 8-10 mo old APP/PS1 mice (WT n =17; rTg4510 n=17 slices). There was no difference in PPR in younger rTg4510 and APP/PS1 mice compared to controls.*

Summary

- At 2-3 mo of age neither basal synaptic transmission nor long-term potentiation is impaired in rTg4510 and APP_PS1 models
- rTg4510 mice do not exhibit basal synaptic transmission impairment even at 6-7 mo of age
- Reduction in fEPSP slope and fiber volley amplitude in rTg4510 mice is probably due to neurodegeneration
- However, paired-pulse facilitation was reduced in rTg4510 mice suggesting some pre-synaptic alteration in remaining neurons
- APP/PS1 mice show reduced basal synaptic transmission at 8-10 mo of age
- Both models exhibit age-dependent long-term potentiation deficits, clearly evident at 6-7 mo in rTg4510 and at 8-10 mo in APP/PS1
- In APP/PS1 mice LTP reduction may be due to induction deficits, since they exhibit reduced basal synaptic transmission and post-tetanic potentiation

References

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