Chronic administration of a new therapeutic agent improves memory in a mouse model of Alzheimer's disease with tau deposition.

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Background

Alzheimer's disease (AD) is characterized clinically by progressive cognitive decline, eventually resulting in death usually within 10 years of diagnosis. To this date, there is no cure to AD. Thus it is essential to find new therapeutic agents to help reducing cognitive impairments and pathology.

Tau hyperphosphorylation and accumulation into intraneuronal neuro-fibrillary tangles are linked to neurodegeneration in Alzheimer's disease and similar tauopathies. We tested the effects of a new agent in Tg4510 mice. These mice develop progressive tau pathology with histologically discernible tau deposits similar to that found in AD patients at 3 months of age, leading to neuronal loss, and atrophy by 6 months of age.

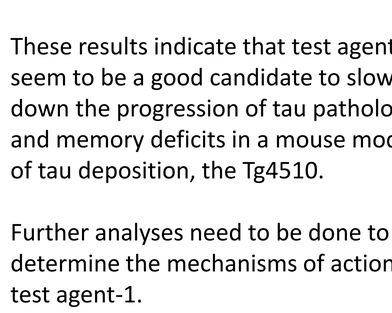
Objective

The aim of this study was to test the effects of a chronic administration of a new therapeutic agent, Test agent-1, in a model of tau deposition (Tg4510 mice) for effects on tau pathology and cognition.

Methods

Tg4510r mice, carrying the human four-repeat tau with the P301L mutation and the CamK-II tetracycline-controlled transactivator protein were used. Non-transgenic littermates were used as control groups for behavioral testing and anatomy comparisons. Starting at 2 mo of age, mice were given either a standard diet or a diet containing Test agent-1 for three months *ad libitum*.

Experimental design



Conclusion

- ✓ Started at 2 mo of age, a special diet containing test agent-1 given for 3 months was able to prevent some memory deficits in Tg4510 mice when compared to standard diet.
- ✓ Analysis of hippocampus homogenates revealed a decrease in tau oligomers in the insoluble fraction of Tg4510 mice treated with test agent-1 compared to standard diet.
- ✓ These results indicate that test agent-1 seem to be a good candidate to slow down the progression of tau pathology and memory deficits in a mouse model of tau deposition, the Tg4510.
- ✓ Further analyses need to be done to determine the mechanisms of action of test agent-1.

Results

1. Treatment with test agent-1 for three months improved memory during Radial arm water maze in Tg4510 mice.

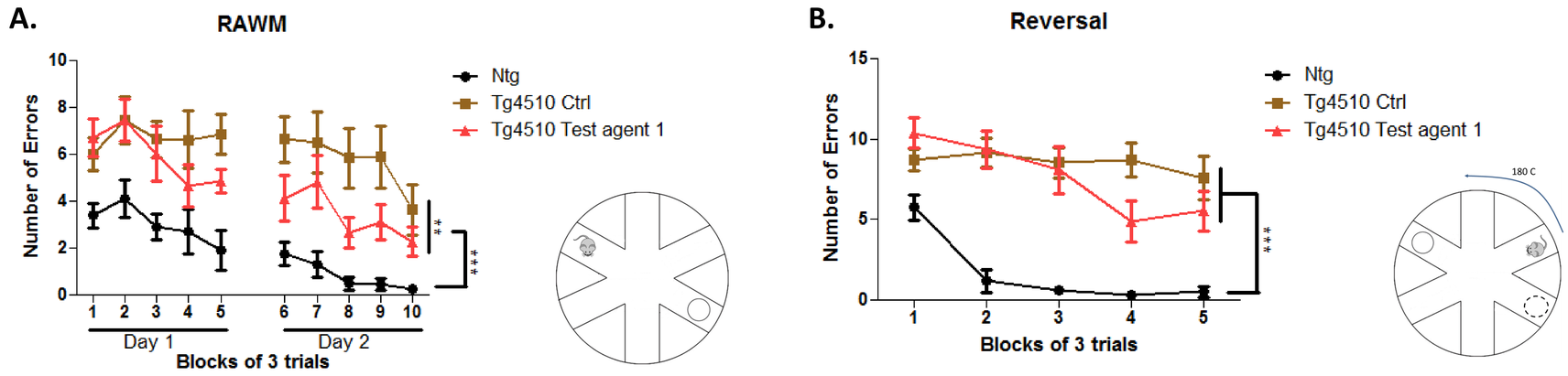


Figure 1.
Radial arm water maze test (RAWM, A) and reversal (B) in non-transgenic littermates (Ntg, black line), tau mice under standard diet (Tg4510 Ctrl, brown line), or special diet containing test agent 1 (Tg4510 Test agent 1, pink line). Data are presented as mean +/- SEM ($p<0.05$*, $p<0.01$**, $p<0.001$***).

2. Improved memory in Tg4510 mice treated with test agent-1 was not associated with a decrease in pathology when assessed by histochemistry.

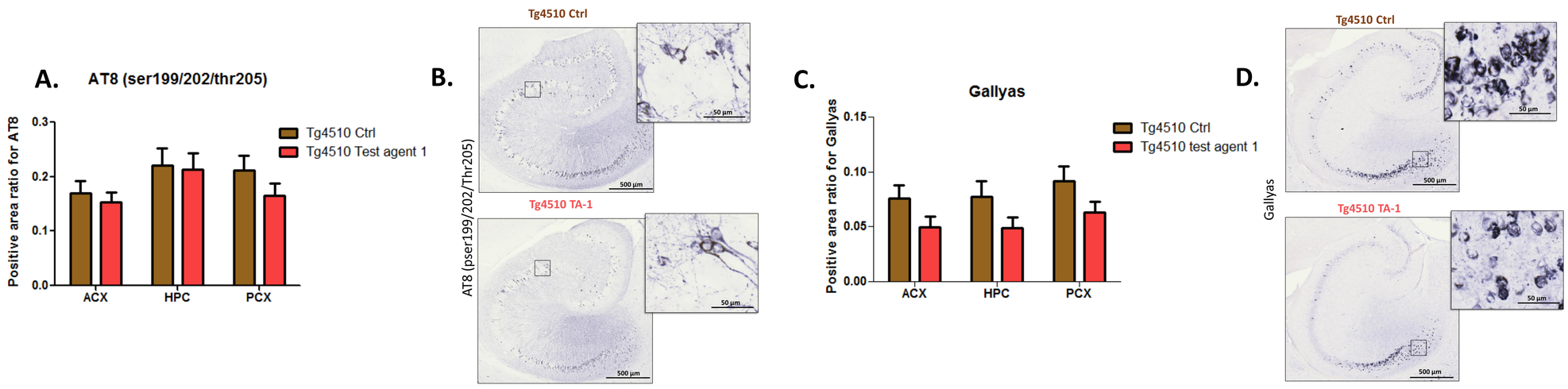


Figure 2.
Percentage of positive staining for phosphorylated tau (AT8, A), and Gallyas stain (C), in anterior cortex (ACX), hippocampus (HPC) and posterior cortex (PCX) area in tau mice under standard diet (Tg4510 Ctrl, brown bars), or special diet with test agent-1 (Tg4510 Test agent 1, pink bars). Micrograph representation of immuno-detection of AT8 (B) and Gallyas (D) in 25 microns horizontal sections of the hippocampus of Tg4510 mice under standard diet (Tg4510 Ctrl), or special diet with test agent-1 (Tg4510 TA-1). Insert is a magnification of square area. As expected no positive staining was observed in non-transgenic mice (data not shown). Data are presented as mean +/- SEM ($p<0.05$*).

3. Tg4510 mice treated with test agent-1 showed a decrease in insoluble tau oligomers in hippocampus homogenates when compared to Tg4510 mice under standard diet.

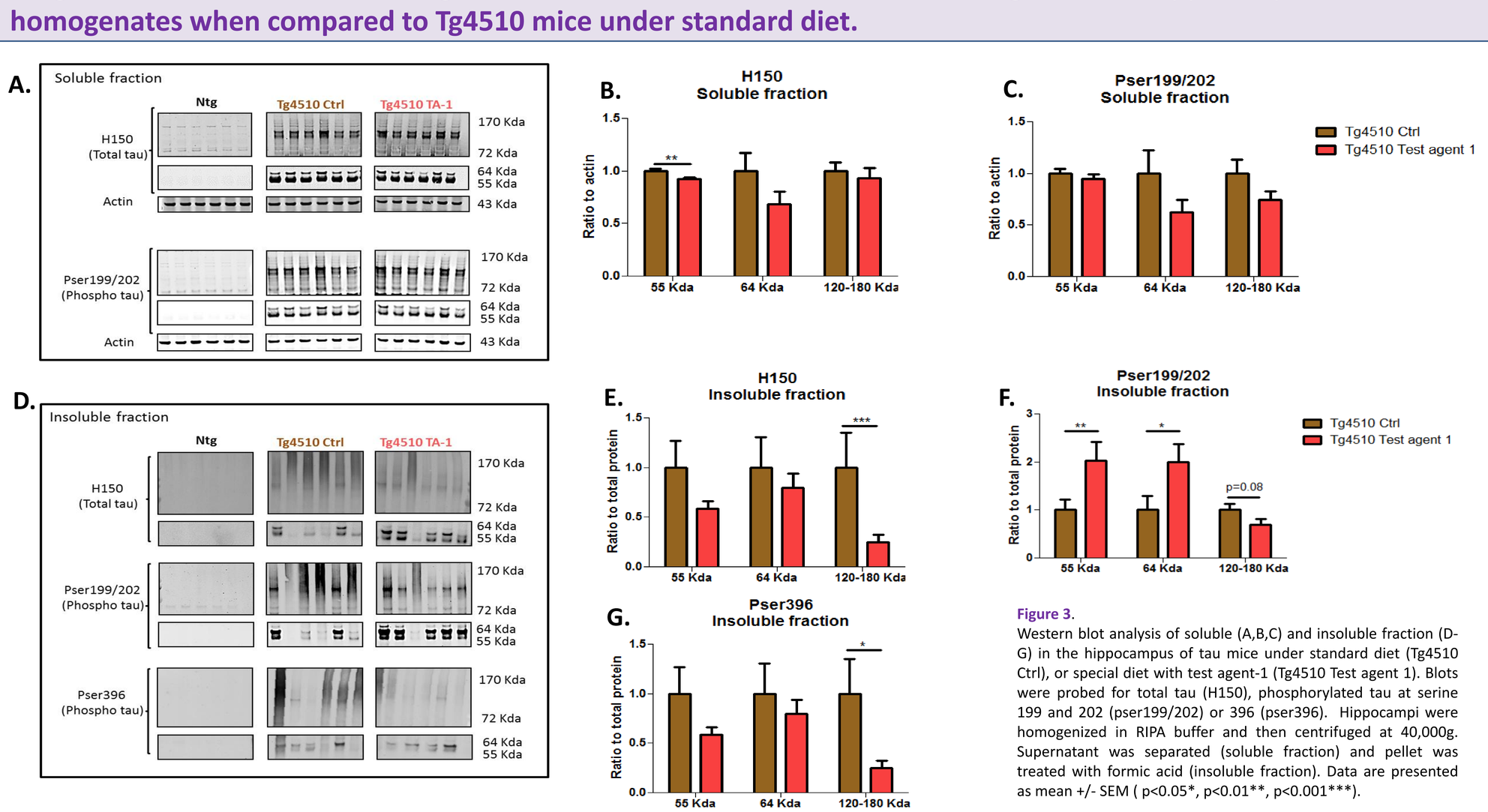


Figure 3.
Western blot analysis of soluble (A,B,C) and insoluble fraction (D-G) in the hippocampus of tau mice under standard diet (Tg4510 Ctrl), or special diet with test agent-1 (Tg4510 Test agent 1). Blots were probed for total tau (H150), phosphorylated tau at serine 199 and 202 (pser199/202) or 396 (pser396). Hippocampi were homogenized in RIPA buffer and then centrifuged at 40,000g. Supernatant was separated (soluble fraction) and pellet was treated with formic acid (insoluble fraction). Data are presented as mean +/- SEM ($p<0.05$*, $p<0.01$**, $p<0.001$***).