Disruption of Normal Circadian Function in a Mouse Model of Tauopathy

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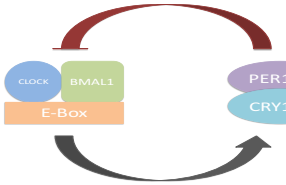
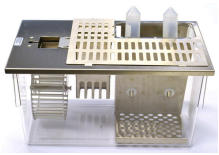
Introduction

Alzheimer's Disease (AD) is a neurodegenerative disease characterized by a deterioration in learning and memory which is often associated with a disruption in the normal circadian rhythm. A circadian rhythm is an endogenous biological timing mechanism that controls various physiological processes, including the sleep/wake cycle, and is characterized by its endogenous free running period which is maintained in the absence of external cues, as well as its ability to be reset by these cues. One of the two hallmarks of AD-associated neuropathy is the accumulation of hyperphosphorylated tau protein, and the further aggregation into toxic neurofibrillary tangles (NFTs)—otherwise known as tauopathy. This study is focused on elucidating how tauopathy disrupts normal circadian clock function at both the behavioral and molecular levels.

The core loop of the circadian clock

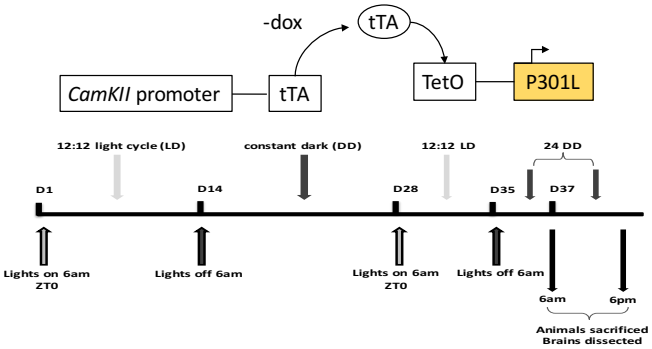


Circadian chambers with activity wheels



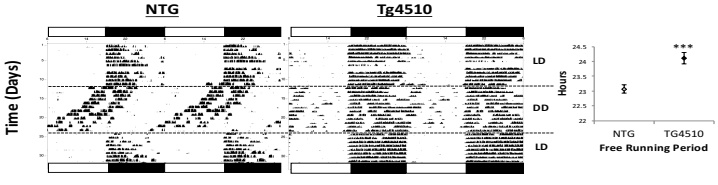
Methods

Tg4510 mice are a double transgenic TET-off model of tauopathy in which the human mutant P301L allele tau (MAPT) is expressed in regions of the brain involved in learning and memory. 3-month and 8-month old male and female Tg4510 mice were housed in circadian chambers that measured activity on running wheels. Western blotting was used to analyze the expression of clock proteins (PER2, BMAL1), phosphorylated tau protein, and total levels of tau.

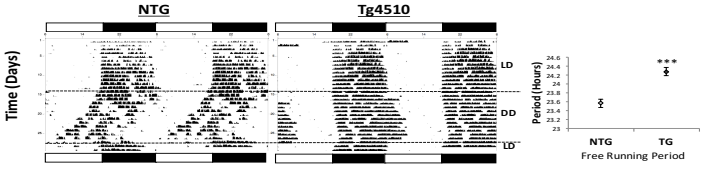


Behavior

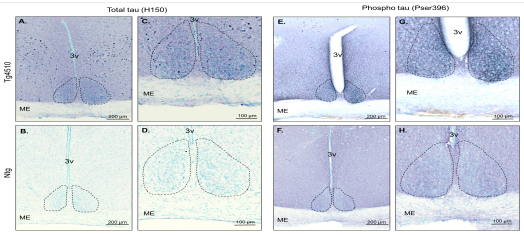
Actogram profiles for 8-month old non-transgenic (Ntg) and transgenic Tg4510 mice. Tg4510 mice show a long free-running period when compared to Ntg (***P<0.001)



Actogram profiles for 3-month old Ntg and Tg4510 mice. 3-month old Tg4510 mice show a longer free-running period when compared to their Ntg littermates (***P<0.001)

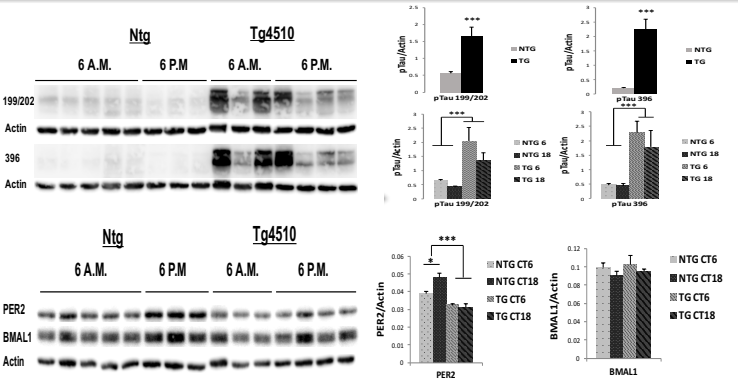


Immunohistochemistry

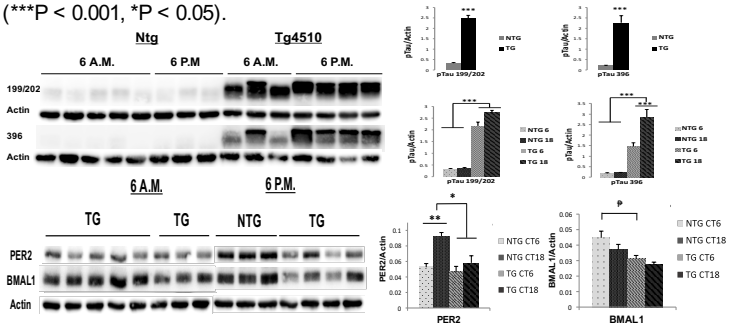


Tg4510 mice show a localization of tau in the suprachiasmatic nucleus (SCN), the location of the central circadian clock.

Immunoblotting



Western blot analysis of hypothalamic tissue shows higher levels of phosphorylated tau in transgenic mice (***P < 0.001). There are also lower PER2 levels and a disrupted PER2 rhythm in Tg4510 tissue compared to Ntg (***P < 0.001, *P < 0.05).



Western blot analysis of hippocampal tissue shows higher level of phosphorylated tau in transgenic mice (***P < 0.001). Results show no BMAL1 rhythm, but a lower level of PER2 and a trend toward a disrupted rhythm of PER2 (P=0.07; **P < 0.01, *P < 0.05). Results also show a lower level of BMAL1 in the transgenic mice when Tg4510 mice are compared to NTG mice at 6 A.M. (*P< 0.05).

Discussion

The behavioral data indicates a connection between the tau pathology and a disruption in circadian rhythms. The longer free running periods in the transgenic mice suggests an alteration in the endogenous circadian rhythm. The disruption of the free running period in the TG4510 mice is seen by the lack of a phase shift in the actogram, while the non-transgenic mice have a defined shift. Additionally, transgenic mice have more bouts during the day than wildtype mice. This hyperactivity can be attributed to disrupted sleep cycles, which are frequently seen in patients with AD. The localization of tau in the hypothalamus, suggests that tau accumulation disrupts the central clock in the SCN. Western blots show alterations in PER2 levels in both hypothalamic and hippocampal tissue. There is also an oscillation of clock protein levels between time points, which we hope to make more clear through further experiments.

Acknowledgments

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