Neurobiology of Disease 114 (2018) 194–200

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Behavioral and SCN neurophysiological disruption in the Tg-SwDI mouse model of Alzheimer's disease

Jodi R. Paul[a], Hira A. Munir[a], Thomas van Groen[b], Karen L. Gamble[a,*]

[a] Department of Psychiatry and Behavioral Neurobiology, University of Alabama at Birmingham, Birmingham, AL, USA
[b] Department of Cell, Developmental, & Integrative Biology, University of Alabama at Birmingham, Birmingham, AL, USA

ARTICLE INFO

Keywords:
Alzheimer's disease
Suprachiasmatic nucleus
Circadian rhythms
A-type potassium current
Electrophysiology

ABSTRACT

Disruption of circadian rhythms is commonly reported in individuals with Alzheimer's disease (AD). Neurons in the primary circadian pacemaker, the suprachiasmatic nucleus (SCN), exhibit daily rhythms in spontaneous neuronal activity which are important for maintaining circadian behavioral rhythms. Disruption of SCN neuronal activity has been reported in animal models of other neurodegenerative disorders; however, the effect of AD on SCN neurophysiology remains unknown. In this study we examined circadian behavioral and electrophysiological changes in a mouse model of AD, using male mice from the Tg-SwDI line which expresses human amyloid precursor protein with the familial Swedish (K670N/M671L), Dutch (E693Q), Iowa (D694N) mutations. The free-running period of wheel-running behavior was significantly shorter in Tg-SwDI mice compared to wild-type (WT) controls at all ages examined (3, 6, and 10 months). At the SCN level, the day/night difference in spike rate was significantly dampened in 6–8 month-old Tg-SwDI mice, with decreased AP firing during the day and an increase in neuronal activity at night. The dampening of SCN excitability rhythms in Tg-SwDI mice was not associated with changes in input resistance, resting membrane potential, or action potential after-hyperpolarization amplitude; however, SCN neurons from Tg-SwDI mice had significantly reduced A-type potassium current (I_A) during the day compared to WT cells. Taken together, these results provide the first evidence of SCN neurophysiological disruption in a mouse model of AD, and highlight I_A as a potential target for AD treatment strategies in the future.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative form of dementia associated with elevated levels of the amyloid β (Aβ) peptide and the formation of pathological Aβ plaques and neurofibrillary tangles (Selkoe 1999). The level of circulating Aβ, which is also found in the cerebrospinal fluid of (CSF) of healthy individuals, is tightly coupled to sleep/wake cycles and is molecular clock-dependent (Kress et al. 2018), with Aβ levels increasing throughout the activity phase of humans and rodents (Kang et al. 2009). Furthermore, prolonged sleep deprivation has been found to potentiate Aβ plaque formation in multiple mouse models of AD (Kang et al. 2009; Roh et al. 2012). Patients with AD often exhibit "sundowning syndrome," a constellation of symptoms including late afternoon/evening delirium, hyperactivity, restlessness, confusion, and aggression, along with misaligned core body temperature and activity rhythms (Volicer et al. 2001; Khachiyants et al. 2011). These symptoms suggest a dysregulated circadian network, which regulates sleep/wake timing and allows anticipation of and preparation for daily recurring environmental events. Indeed, circadian rhythm disruption has been demonstrated in numerous mouse models of AD (Sterniczuk et al. 2010; Stranahan 2012; Coogan et al. 2013; Oyegbami et al. 2017).

In mammals, the primary circadian pacemaker is located in the suprachiasmatic nucleus (SCN) of the hypothalamus. SCN neurons exhibit daily rhythms in spontaneous action potential (AP) firing which are critical for robust and consolidated circadian behavior (Schwartz et al. 1987). Loss or dampening of SCN neuronal activity rhythms has been described in animal models of other neurodegenerative disorders (Kudo et al. 2011a; Kudo et al. 2011b) and aging (Nakamura et al. 2011; Farajnia et al. 2012); however, changes in SCN neurophysiology in AD models have not yet been examined. Therefore, in the present study, we sought to determine whether changes in SCN neuronal excitability are associated with circadian behavioral disruption in a mouse model of AD and to identify the ionic mechanism driving these neurophysiological changes.

* Corresponding author at: Department of Psychiatry and Behavioral Neurobiology, University of Alabama at Birmingham, 1720 7th Ave S., Birmingham, AL 35294, USA.
E-mail address: klgamble@uab.edu (K.L. Gamble).

https://doi.org/10.1016/j.nbd.2018.03.007
Received 7 September 2017; Received in revised form 1 March 2018; Accepted 10 March 2018
Available online 11 March 2018
0969-9961/

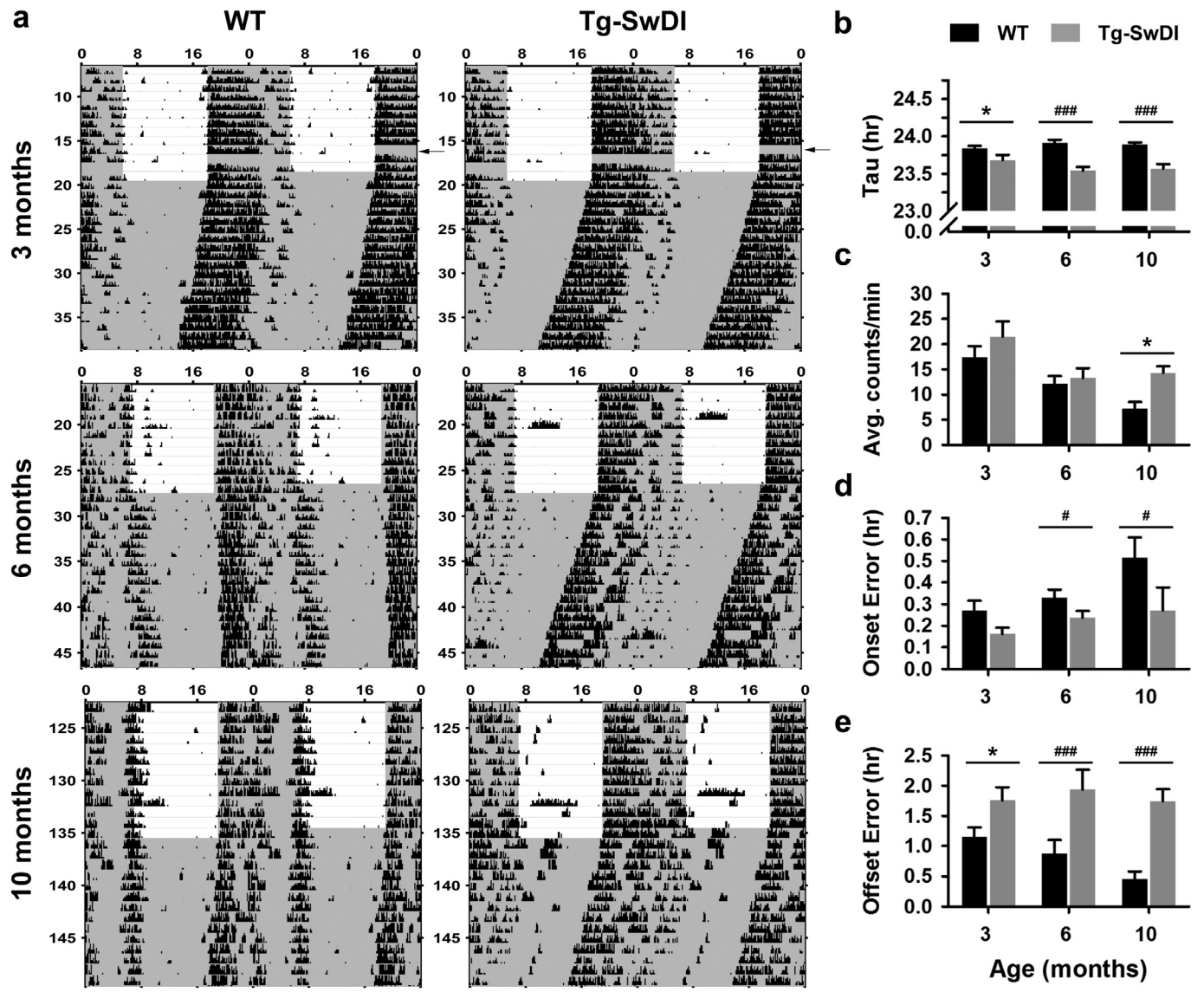

Fig. 1. Period of circadian behavioral rhythms is shortened in Tg-SwDI mice at all examined ages. (a) Representative double plotted actograms of wheel-running activity for WT (left) and Tg-SwDI mice (right) at 3, 6 and 10 months of age beginning in LD and then released into DD. The arrow denotes loss of 24-h data due to computer malfunction which did not impact the LD cycle. (b–e) Quantification of behavioral rhythms in DD at each age. Bar graphs indicate means ± SEM of free-running period (b), average activity (c), interdaily variability of activity onset (d) and offset (e). Symbols denote significant difference between genotypes at one age ($^{*}p < 0.05$) or significant main effect of genotype for 6 and 10 months animals ($^{\#}p < 0.05$ or $^{\#\#\#}p < 0.001$). n = 6–7 mice per genotype, per age.

2. Materials and methods

2.1. Animals

Male mice expressing the human amyloid precursor protein with the familial Swedish (K670 N/M671 L), Dutch (E693Q), Iowa (D694N) homozygous mutations (Tg-SwDI; (Davis et al. 2004); commercially available from Mutant Mouse Research and Resource Center JAX or MMRRC; Stock #034843), congenic on a C57-BL6/J background, were bred within the University of Alabama at Birmingham (UAB) animal colony and compared to age-matched C57-BL6/J wild-type (WT) mice (generated within the colony or purchased from Jackson Laboratories, Bar Harbor, ME) for all experiments. Female mice were not used to avoid the potential effect of estrous on circadian behavior (Leise and Harrington 2011) and A-type potassium current (I_A; (Pielecka-Fortuna et al. 2011)). Animals were housed in a 12:12 light/dark cycle (LD) or constant dark (DD) with food and water *ad libitum* in accordance with UAB IACUC guidelines and the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978). All animals were euthanized with cervical dislocation and rapid decapitation. For loose-patch experiments, mice were individually housed in cages with running wheels for at least three weeks in DD and sacrificed and enucleated in the dark with the aid of night-vision goggles at circadian time (CT; where CT 12 is defined as the onset of activity) 4 or 16. For whole-cell recordings, mice were group-housed in LD and sacrificed between Zeitgeber time (ZT; where ZT 0 equals time of lights-on) 1–2 for day recordings or 11–12 for night recordings.

2.2. Behavior

Mice were individually housed with running wheels starting at 3 months or 6 months of age. The same animals were used for the 6 and 10 month old behavioral measurements, and the animals were re-entrained to LD for at least 1 month prior to beginning behavioral measurements at 10 months of age. Wheel-running activity was recorded and analyzed using ClockLab software (Actimetrics, Wilmette, IL) as described previously (Paul et al. 2012). Behavior was analyzed across