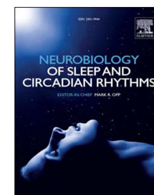
Neurobiology of Sleep and Circadian Rhythms 2 (2017) 27–38

Contents lists available at ScienceDirect

Neurobiology of Sleep and Circadian Rhythms

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



Research paper

Prolonged day length exposure improves circadian deficits and survival in a transgenic mouse model of Huntington's disease

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ARTICLE INFO

Keywords:
Transgenic mouse
Sleep
Estrogen
Lifespan
Depression

ABSTRACT

The circadian disruption seen in patients of Huntington's disease (HD) is recapitulated in the R6/2 mouse model. As the disease progresses, the activity of R6/2 mice increases dramatically during the rest (light) period and decreases during the active (dark) period, eventually leading to a complete disintegration of rest-activity rhythms by the age of ~16 weeks. The suprachiasmatic nucleus controls circadian rhythms by entraining the rest-activity rhythms to the environmental light-dark cycle. Since R6/2 mice can shift their rest-activity rhythms in response to a jet-lag paradigm and also respond positively to bright light therapy (1000 lx), we investigated whether or not a prolonged day length exposure could reduce their daytime activity and improve their behavioural circadian rhythms. We found that a long-day photoperiod (16 h light/8 h dark cycle; 100 lx) significantly improved the survival of R6/2 female mice by 2.4 weeks, compared to mice kept under standard conditions (12 h light/12 h dark cycle). Furthermore, a long-day photoperiod improved the nocturnality of R6/2 female mice. Mice kept under long-day photoperiod also maintained acrophase in activity rhythms (a parameter of rhythmicity strength) in phase with that of WT mice, even if they were symptomatic. By contrast, a short-day photoperiod (8 h light/16 h dark cycle) was deleterious to R6/2 female mice and further reduced the survival by ~1 week. Together, our results support the idea that light therapy may be beneficial for improving circadian dysfunction in HD patients.

1. Introduction

Huntington's disease (HD) is a genetic neurodegenerative disorder characterised by motor, cognitive and psychiatric symptoms. It is now well-established that sleep disruption and circadian abnormalities are symptoms associated with HD (for references, see Morton (2013)). Disrupted rest-activity patterns observed in HD patients are recapitulated in multiple HD mice models (Morton et al., 2005; Kudo et al., 2011; Loh et al., 2013; Fisher et al., 2013, 2016). The R6/2 line of HD mice with 250 CAG repeats exhibits a rapid progression in neurological pathology that starts at ~6 weeks of age, and causes an early death at ~22 weeks of age (Wood et al., 2013). The circadian abnormalities appear from the age of 10–12 weeks and result in a complete disintegration of daily cycles by the age of 15–16 weeks (Wood et al., 2013).

The circadian dysrhythmia in R6/2 mice is accompanied at the molecular level by a temporal dysregulation of the clock genes in the suprachiasmatic nucleus (SCN) and clock-dependent genes in peripheral tissues (Morton et al., 2005; Maywood et al., 2010). However, the molecular machinery in the SCN of arrhythmic 16 week old R6/2 mice remains intact; when the SCN from arrhythmic R6/2 mice were studied *ex vivo*, they expressed normal electrophysiological output and normal endogenous rhythms of circadian gene expression (Pallier et al., 2007). This suggested that rather than being 'broken', the SCN is functionally dysregulated *in vivo* by pathological afferent input. Given that the molecular machinery is intact, the SCN should be able to respond when stimulated appropriately. In support of this idea, it has been shown that pharmacological (Pallier et al., 2007) as well as non-pharmacological interventions (e.g. temporally scheduled feeding (Maywood et al., 2010) and bright light therapy associated with exercise (Cuesta et al., 2014)) are able to improve the rest-activity rhythms of symptomatic R6/2 mice.

In mammals, circadian rhythms are regulated via direct input from retinal photoreceptors to the SCN. Retinal degeneration and functional impairment have been reported in the R6 lines (Helmlinger et al., 2002; Petrasch-Parwez et al., 2004; Batcha et al., 2012; Ragauskas et al., 2014; Ouk et al., 2016), leading possibly to visual and non-visual dysfunctions such as circadian photoreception. However, we have

Abbreviations: ANOVA, analysis of variance; DD, constant darkness; EEG, electroencephalography; HD, Huntington's disease; HPA axis, hypothalamic-pituitary-adrenal axis; LD, light-dark; L-DOPA, levodopa; REM sleep, rapid eye movement sleep; SCN, suprachiasmatic nucleus; WT, wild type

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http://dx.doi.org/10.1016/j.nbscr.2016.11.004
Received 21 July 2016; Received in revised form 25 October 2016; Accepted 22 November 2016
Available online 30 November 2016
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shown that R6/2 mice are able to respond to photic manipulations such as 6 h jet-lag paradigm as well as 23 h-day (with light exposure at 100 lx) (Wood et al., 2013). We have also seen that the photoreceptors responded to bright light therapy at 1000 lx (Cuesta et al., 2014). Therefore, in the present study we manipulated the light/dark (LD) cycles by changing the photoperiod length as a way to modify the rest-activity rhythms of R6/2 mice.

Under the standard 12 h light/12 h dark cycle, R6/2 mice show a breakdown in their rest-activity rhythms from around 15–16 weeks (Wood et al., 2013), accompanied with a progressive general health deterioration and loss of body weight. In this study, we hypothesised that a prolonged daily light exposure would reduce aberrant daytime activity. We tested the effect of a long-day photoperiod (16 h light/8 h dark cycle) on the rest-activity rhythms, body weight and survival of R6/2 mice. For comparison, we also tested R6/2 mice under a short-day photoperiod (8 h light/16 h dark cycle) and a standard photoperiod (12 h light/12 h dark cycle).

2. Material and methods

2.1. Ethic statement

All experiments were carried out in accordance with the UK Animals (Scientific Procedures) Act 1986, and with the approval of the University of Cambridge Animal Welfare and Ethical Review Board.

2.2. Animals and housing conditions

Wild type (WT) and R6/2 mice were taken from a colony established in the University of Cambridge (CBA x C57BL/6J background) and obtained following the breeding strategy used by Prof. Gill Bates group (Mangiarini et al., 1996). The genotype and the number of CAG repeats of each mouse were determined from tail snips by Laragen (Los Angeles, USA) using GeneMapper (Morton et al., 2009) before, and verified after, the experiments. The 72 R6/2 mice used in the whole study had a mean CAG repeat length of 250 ± 1.

Prior to the experiments, mice were kept in their home cage, with a maximum of 10 animals of the same sex and genotype in each cage. The mice were maintained in a controlled environment with 12:12 light-dark cycle, room temperature of 21–23 °C and humidity of 55% ± 10, and had *ad libitum* access to dry laboratory food and water. All mice were transferred to clean cages once weekly.

During the circadian studies, mice were housed individually in a light-tight and sound-proof Scantainer ventilated cabinet (Scanbur, Denmark) with controlled humidity (55% ± 10) and temperature (21–23 °C), and a built-in light system (100 lx). Mice had *ad libitum* access to food and water, which was delivered by lowered bottles with elongated spouts to facilitate access for symptomatic R6/2 mice. The activity of the mice was checked daily and the mice were visually examined twice a week. As an indication of general well-being, mice were weighed once a week throughout the study and then twice weekly once the body weight of R6/2 mice started to decrease.

2.3. Analysis

Activity of the mice in circadian cages was recorded continuously throughout the experiment with motion sensors (Bosch, Germany) placed on top of each cage and connected to a computerised recording system (Clocklab; Actimetrics, Evanston, IL, USA). Total activity data were double plotted in actograms using 5-min bins. All behavioral analyses were performed using Clocklab software. Period length was calculated using a least-square fits regression line using 7 continuous activity onsets. The Chi-squared periodogram function of Clocklab was used to verify strength of rhythmicity using a line of significance at 0.001. Duration of the active period (alpha) was calculated as the difference between the means of the regression lines drawn through the activity onsets and corresponding offsets. The distribution of the general activity during the active and rest periods was determined using the profile activity function of the software. Rest-activity ratios were calculated as the amount of activity occurring during the light period as a fraction of the amount of activity occurring during the nocturnal activity. Phase angle of activity to light onset and offset was calculated to determine the entrainment of the circadian locomotor activity rhythms to the light-dark schedule. For this, we determined mean time of day when mice were starting (or ending) their activity phase using least-square regression lines fitted to the activity onsets (or offsets) of the targeted time span. We then calculated the time difference with local time when lights were on (or off). Time of activity onsets and offsets were also verified from the analysis of the profile activity. Only rhythmic mice were included in the analysis. Acrophase (peak time) in activity rhythms, a parameter of rhythmicity strength, was estimated using Clocklab function by fitting the activity of each day to a sine function with a period of 24 h. For each parameter, data were averaged across 7 consecutive days. General activity during active and rest period was determined using the profile activity function of the software.

2.4. Lighting conditions

All the mice were first placed in the circadian cabinet at 8 weeks of

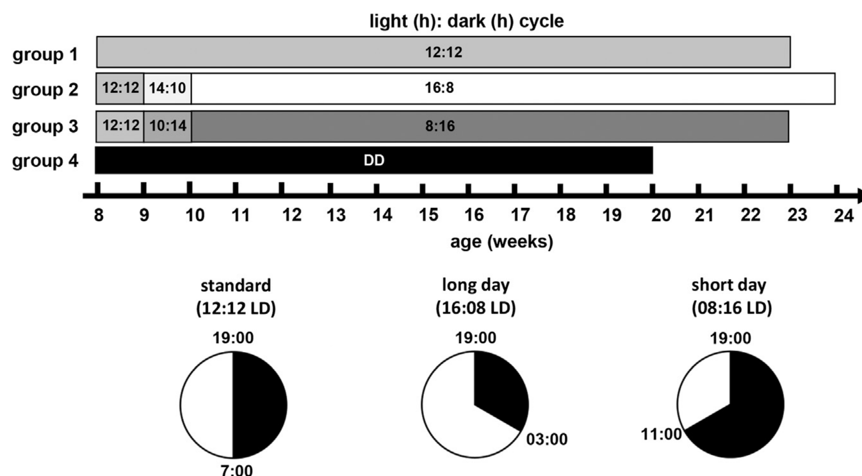

Fig. 1. Experimental time and light schedule for photoperiod testing. Circadian data were collected from mice placed under four different photoperiod lengths: standard condition (12:12 LD cycle), long-day photoperiod (16:8 LD cycle), short-day photoperiod (8:16 LD cycle) and DD (constant darkness). Lights off was set at the same local time of 19:00 for standard, long- and short-day photoperiods.

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