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Circadian rhythms in SAMP8: a longitudinal study of the effects of age and experience

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Abstract

Age-related effects on circadian rhythms include reductions of rhythm amplitude, alterations in re-entrainment, and increased fragmentation. Currently, the pattern of these changes across an individuals' lifespan is unknown. The present study used a cross-sequential experimental design to determine the pattern of circadian rhythm changes, identify predictors of later circadian rhythm disruption, and assess the effect of prior run-wheel experience on circadian rhythms. Run-wheel activity was assessed in senescence-accelerated mice (SAMP8) at 2, 7, and 12 months of age. Age-related changes included decrease of run-wheel activity, decrease in circadian rhythm amplitude, increase in proportion of light activity, and increase in split activity rhythms. Proportion of light activity at 2 months was a good predictor of circadian rhythm disruption at 7 months. Run-wheel experience increased overall activity and decreased proportion of light activity, but did not alter rhythm amplitude or period. These results demonstrate that aging produces several patterns of circadian rhythm changes, describe predictive measures of future rhythm disruptions, and suggest an intervention to reduce circadian rhythm disruptions.

Keywords: Circadian rhythms; Aging; Senescence-accelerated mouse; SAMP8; Split activity rhythms

1. Introduction

Age-related disruptions of circadian rhythms are a common occurrence in many species. In elderly humans, rhythm disturbances include altered sleep–wake patterns, weak coupling with environmental rhythms, reduced daytime cognitive performance, and increased nighttime activity [27,29,31]. Similar behavioral changes occur in aged animals [25,33]. These changes in circadian rhythms may, at least in part, contribute to the cognitive and physical impairments observed in aged individuals [1].

The senescence accelerated mouse line (SAM) developed by Takeda and associates is one of several animal models of aging [23,24]. Mice of this line were selectively bred for differences in a senescence score [9], lifespan and pathologic phenotypes [22]. Currently, sub-lines of SAM differ in the rate of aging for various phenotypes. The P8 sub-line (SAMP8) has been investigated for its early onset of age-related disruptions of learning, memory and circadian rhythms [22]. The SAMP8 are frequently compared to the SAMR1, a sub-line that was selected for resistance to age-related disruptions.

In SAMP8, age-related changes in circadian rhythms include a reduction in amplitude and increased fragmentation [2,10–12,18,20,22]. These age-related changes are characteristic of those observed in the aging process of other animals, including humans [4,15,30,32,33]. Furthermore, these changes of circadian rhythms are accelerated in SAMP8 as compared to SAMR1 [2,11,12,18]. With the SAMP8, a lengthened free-running period has also been reported, but the evidence for this is mixed [2,10,18]. An age-induced lengthening of free-running period differs from that observed with some other animals. For instance, rodents such as hamster, rat and deer–mice show a shortening of their free-running period with age rather than a lengthening [13,14,17,26].

Some aspects of activity rhythms in SAMP8 appear to be unusual regardless of age. Recently, we reported that some older SAMP8 produce split activity rhythms [10]. This splitting of activity rhythms resulted in a secondary peak of activity at approximately 12 h intervals and decreased the amplitude of the primary peak at approximately 24 h. SAMP8 also show a faster rate of re-entrainment following a phase advance, an overall higher level of locomotor

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activity, and a higher proportion of activity during the normally inactive light phase when compared to age-matched SAMR1 [11,12,18]. Disruptions of this sort in the normal pattern of rodent locomotor activity are reminiscent of various rhythm disorders associated with human aging. For example, patients with senile dementia in particular, show excessive levels of nighttime activity, in relation to healthy elderly of the same age [19,29].

To date, most studies of the effects of aging on circadian rhythms have involved cross-sectional experimental designs. Although cross-sectional designs are useful for investigating the effects of age of a population of animals, they are not designed to assess patterns of change that occur across the lifespan of an individual. Longitudinal designs, thus, make it possible to determine whether or not the aging process produces consistent alterations in circadian rhythms, which might be masked by between-group variability in a cross-sectional design. Additionally, longitudinal assessments may help to identify measures in young subjects that predict the early onset of circadian rhythm disruptions. These predictive measures may be useful for developing early interventions that are designed to prevent or delay age-related disruptions of circadian rhythms.

The few longitudinal animal studies that have examined age-related changes of circadian rhythms have used hamsters [5,7,13]. In these studies, general activity levels and the incidence of rhythm splitting decreased with age. These studies differed in their findings with respect to free-running period, with two studies reporting no change [5,7] and one concluding a shortening of the free-running period with age [13]. To our knowledge, longitudinal studies using species other than the hamster have not been reported. Such studies, however, are necessary to determine the generality of the age-related effects observed in hamsters.

The SAMP8 provides an excellent animal model for a longitudinal assessment of circadian rhythms because these mice age rapidly, requiring a relatively short study length, and demonstrate clear changes in circadian rhythm measures that are characteristic of those frequently considered part of the normal aging process in animals, including humans [2,10,18]. The present study investigated the circadian rhythms of wheel-running activity in SAMP8 using a cross-sequential design. A cross-sequential design combines both cross-sectional and longitudinal components. Circadian rhythms were initially assessed in three groups of naïve mice that were ages 2, 7, and 12 months. The mice initially tested at 2 months were then re-tested at 7 and 12 months, and the mice initially tested at 7 months were then re-tested at 12 months, forming the longitudinal component of the study. This design permitted both an assessment of circadian rhythm changes across the lifespan of the SAMP8 and an assessment of the impact of run-wheel experience early in life on circadian rhythm disruptions later in life. The effect of run-wheel experience was examined primarily by comparing the circadian rhythms of the naïve 12-month-old SAMP8 with those that had been tested previously once (at 7 months) or twice (at 2 and 7 months).

2. Method

2.1. Animals

Twenty-five male SAMP8 were subjects for the study; eight were tested at 2, 7, and 12 months of age, six were tested at 7 and 12 months of age, and eleven were tested at only 12 months of age. Mice were bred and raised in the animal research facility at Bowling Green State University. Two to four same-sex littermates were housed together, with food and water available ad libitum. Lights in the animal rooms were on a 12:12 h light–dark cycle (lights on at 7:30 a.m.). All procedures followed the NIH guidelines for handling and caring for animals and were approved by the Bowling Green State University Animal Care & Use Committee.

2.2. Apparatus

Wheel-running activity was monitored using four Wahmann running wheels (110 cm circumference, 7.5 cm width) located in a room separate from the animal colony room. The room was illuminated at 165 lux during the light phase. A cage (22.5 cm × 12.5 cm × 12.5 cm) was attached to each wheel, containing food and water. Mice were able to move freely between the cage and the wheel. An IBM compatible computer with custom designed software recorded the activity of each wheel by recording the time of each wheel revolution. A magnet attached to the wheel's axis of rotation closed a switch, signaling to the computer that a wheel revolution occurred.

2.3. Procedure

During testing, wheel-running activity was monitored for 16 days. For the first 6 days, mice were monitored on a 12:12 h light–dark (LD) cycle to determine a baseline measure of the entrained wheel-running rhythm (τ_{LD}). The onset and offset of light during LD coincided with the light–dark cycle of the animal colony room. For the remaining 10 days, mice were kept in constant darkness (DD) to estimate the period of their free-running rhythms (τ_{DD}).

2.4. Data analysis

Eight SAMP8 were examined at 2, 7, and 12 months of age and comprise the subject pool for analysis of age-related changes in circadian rhythms. To examine the effects of run-wheel experience on circadian rhythms, 12-month SAMP8 were examined after 0 (tested at 12 months of age), 1 (tested at 7 and 12 months) or 2 (tested at 2, 7, and 12 months) prior experiences in the running wheels.