Chronobiology International, Early Online: 1–8, (2013)

ISSN: 0742-0528 print / 1525-6073 online
DOI: 10.3109/07420528.2013.803196

informa
healthcare

Dim Light at Night Does Not Disrupt Timing or Quality of Sleep in Mice

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Artificial nighttime illumination has recently become commonplace throughout the world; however, in common with other animals, humans have not evolved in the ecological context of chronic light at night. With prevailing evidence linking the circadian, endocrine, immune, and metabolic systems, understanding these relationships is important to understanding the etiology and progression of several diseases. To eliminate the covariate of sleep disruption in light at night studies, researchers often use nocturnal animals. However, the assumption that light at night does not affect sleep in nocturnal animals remains unspecified. To test the effects of light at night on sleep, we maintained Swiss-Webster mice in standard light/dark (LD) or dim light at night (DLAN) conditions for 8–10 wks and then measured electroencephalogram (EEG) and electromyogram (EMG) biopotentials via wireless telemetry over the course of two consecutive days to determine differences in sleep timing and homeostasis. Results show no statistical differences in total percent time, number of episodes, maximum or average episode durations in wake, slow-wave sleep (SWS), or rapid eye movement (REM) sleep. No differences were evident in SWS delta power, an index of sleep drive, between groups. Mice kept in DLAN conditions showed a relative increase in REM sleep during the first few hours after the dark/light transition. Both groups displayed normal 24-h circadian rhythms as measured by voluntary running wheel activity. Groups did not differ in body mass, but a marked negative correlation of body mass with percent time spent awake and a positive correlation of body mass with time spent in SWS was evident. Elevated body mass was also associated with shorter maximum wake episode durations, indicating heavier animals had more trouble remaining in the wake vigilance state for extended periods of time. Body mass did not correlate with activity levels, nor did activity levels correlate with time spent in different sleep states. These data indicate that heavier animals tend to sleep more, potentially contributing to further weight gain. We conclude that chronic DLAN exposure does not significantly affect sleep timing or homeostasis in mice, supporting the use of dim light with nocturnal rodents in chronobiology research to eliminate the possible covariate of sleep disruption.

Keywords: Circadian, EEG, EMG, light at night, REM sleep, sleep, slow-wave sleep

INTRODUCTION

Artificial nighttime illumination has become ubiquitous throughout much of the world. However, humans, as well as other animals, have not evolved in this ecological context. The comparatively recent (past 100 yrs) experience of chronic exposure to light at night may therefore influence physiology and behavior through disruption of the parallel circadian and sleep systems (Navara & Nelson, 2007). Accumulating evidence has linked the circadian system with the immune (for review, see Scheiermann et al., 2013) and metabolic (Cho et al., 2012; Fonken et al., 2010; Yang et al., 2006) systems, as well as alterations in affective behavior (Bedrosian et al., 2011a, 2012; LeGates et al., 2012; McClung, 2007; Stephenson et al., 2012). Understanding these connections is important for elucidating complex disease etiology and progression.

Due to the complex and reciprocal interactions between homeostatic sleep processes and circadian systems (Borbély, 1982; Dijk & Archer, 2009), researchers interested in behavioral phenomena related specifically to circadian disruption often choose to work with nocturnal animals to minimize the potential covariate of sleep disturbance (e.g., Bedrosian et al., 2011b; Frank et al., 2010; Fonken et al., 2010; LeGates et al., 2012; Suboni & Yan, 2010). The assumption that chronic dim light at night does not disturb sleep in nocturnal animals has to our knowledge not been tested.

Nocturnal rodents exposed to chronic dim light at night (DLAN) (~5 lux) display normal circadian activity rhythms, but display a suite of altered metabolic (Blask et al., 2011; Fonken et al., 2010), immune (Bedrosian et al., 2011b), and affective (Bedrosian et al., 2011a; Fonken & Nelson, 2013) phenotypes. Furthermore,

Submitted March 4, 2013, Returned for revision May 1, 2013, Accepted May 4, 2013

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animals maintained in DLAN conditions display blunted core clock protein expression rhythms in the hippocampus and suprachiasmatic nucleus (SCN) and a dampened diurnal rhythm in circulating cortisol concentrations (Bedrosian et al., 2013). We therefore investigated the influence of DLAN on sleep and circadian activity rhythms in Swiss-Webster mice utilizing wireless telemetry of electroencephalogram (EEG) and electromyogram (EMG) biopotentials and running wheel activity levels. These data were used to determine whether alterations in sleep timing or quality contribute to the aforementioned deleterious phenotypes displayed in DLAN-exposed animals.

MATERIALS AND METHODS

Animals and Light/Dark Schedule

Twenty male Swiss-Webster mice were singly housed upon arrival to our laboratory and placed on a 14:10 light/dark schedule. Animals were placed in polypropylene cages ($27.8 \times 7.5 \times 13$ cm) in sound-attenuating ventilated cabinets maintained at $24 \pm 2^{\circ}$C. After 1 wk, two groups (10 mice per group) were formed randomly by assigning mice to either a light/dark (LD) or light/dim light at night group (DLAN). Lighting schedules of either 14 h light/10 h dark (150 lux/0 lux) or 14 h light/10 h dim light (150 lux/$\sim$5 lux) were used for the remainder of the study (lights on: 02:00 h; lights off: 16:00 h). Animals were supplied cotton nesting material weekly and food and water ad libitum (Harlan-Teklad no. 8640; Harlan Laboratories, Indianapolis, IN, USA). Mice were given free access to a running wheel to record circadian rhythms in activity. The animals were weighed once a week during the light phase, and cages were changed at this time as well. Otherwise, they were undisturbed. This study was conducted under approval of The Ohio State University Institutional Animal Care Committee and procedures followed the National Institutes of Health *Guide for the Use and Care of Laboratory Animals* and international ethical standards (Portaluppi et al., 2010).

Electroencephalogram and Electromyogram

After approximately 8 wks in their respective lighting conditions, mice were surgically implanted with PhysioTel F20-EET biotelemetry transmitters (Data Sciences International [DSI], St. Paul, MN, USA) according to the manufacturer's protocol (DSI EET Device Surgery Manual) and described in Ashley et al. (2012). This transmitter simultaneously measures electroencephalogram (EEG) and electromyogram (EMG) biopotentials. Mice were deeply anesthetized with isoflurane (5% induction, 1.5% maintenance) and immobilized in a stereotaxic apparatus. A midline incision from the posterior margin of the eyes to midway between the scapulae was made, and the skull was exposed and cleaned. Two stainless steel screws (00-96 $\times$ 1/16; Plastics One, Roanoke, VA, USA) served as cortical electrodes and were inserted through the skull to make contact with the dura mater. The first screw was positioned 1 mm lateral to the sagittal suture and 1 mm anterior to bregma; the second screw was placed contralaterally 2 mm from the sagittal suture and 2 mm posterior to bregma. The transmitter was inserted into a subcutaneous pocket along the back with biopotential leads oriented cranially. One set of leads was attached to screws and secured with dental acrylic; the other set was directly inserted into the cervical trapezius muscles for measurement of EMG. Supplemental warmth and analgesia (buprenorphine) were administered after surgery. Animals were allowed to recover in their respective light conditions for >10 d before recordings began.

Experimental Protocol

Following surgical implantation of the transmitters, individual mouse cages were placed on top of receiver boards (RPC-1; DSI) in their original ventilated cabinets. These boards relay telemetered data from the transmitter to a data exchange matrix (DSI) and a computer running Dataquest A.R.T. software (version 4.1; DSI, St. Paul, MN, USA). EEG and EMG traces were measured for 48 h (starting at 11:00 h). Recordings were terminated after 48 h, and mice were killed the following day. Because the transmitters are activated and deactivated by a magnet, running wheels (that contain magnetic components) were removed from cages prior to sleep recording.

Data Analyses

Circadian rhythms in locomotor activity were analyzed using ClockLab (Coulbourn Instruments, Whitehall, PA, USA) toolbox for MATLAB (MathWorks, Natick, MA, USA). Average wheel rotations per minute, rotations during the light and dark phases, total number of rotations, and percent of rotations in the light phase were determined for each animal and then compared between light conditions with one-way analysis of variance (ANOVA). To determine whether each animal had a normal circadian rhythm in activity, actograms were plotted and visually inspected, and fast Fourier transform (FFT) of tau values of 0.042 ($\sim$1/24) were used as determinants of a 24-h rhythm. Two animals (DLAN 3 and DLAN 7) did not display 24-h rhythms in activity and were therefore excluded from subsequent analysis. This was likely due to higher relative resistances in these running wheels, because upon inspection, these wheels seemed to not rotate as easily as the others, and may have been too hard to run on for these mice.

EEG and EMG files were transferred into Neuroscore software (DSI) and visually inspected for EEG and EMG signal strength. On the first recording day, the building's power supply was tested, and our recording computer lost power for $\sim$3 h (between 06:00 and 09:00 h). Therefore, only the second 24 h of recording were used in analysis. For vigilance state scoring, 10-s epochs of EEG and EMG signals were displayed on the computer

monitor. Then the EEG/EMG data were classified into one of three vigilance states or artifact. These states were scored automatically by Neuroscore software following the default settings for small rodents and were divided into states following Mavanji et al. (2010): (1) Wake: characterized by low-voltage fast EEG, and sustained medium- to high-voltage EMG signals; (2) Slow-wave sleep (SWS): characterized by spindling and high-voltage EEG, and low-voltage EMG; and (3) Paradoxical (REM) sleep: low-voltage fast EEG and low-voltage EMG. Artifact thresholds were set to 0.2 mV for EEG and 1 mV for EMG, and if >10% of the EEG or EMG signal exceeded the threshold, the epoch was scored as artifact. Percent of total time was calculated based on number of 10-s epochs spent in each vigilance state over the course of the 24-h recording period. The total number and mean + maximum durations of each sleep/wake episode for each behavioral state were also calculated. For comparisons of measures across the recording period, 10-s bins were averaged into 30-min epochs for data analysis and visualization.

The following measures were then quantified for group comparisons and repeated-measures analysis: (a) REM sleep, SWS, and wake time; (b) REM sleep, SWS, and wake number of bouts; (c) REM sleep, SWS, and wake average and maximum bout durations; and (d) delta power of SWS.

Statistical analyses were conducted using SPSS Statistics version 20 (IBM, Armonk, NY, USA), and visualized using GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA). To determine differences within sampling periods (across epochs), repeated-measures analysis of variance (ANOVA) was performed with epoch number as the within-subjects variable and lighting condition as the between-subjects variable. Resultant means for each epoch were transferred into GraphPad with corresponding standard error mean values for visualization. For comparison between total mean values between lighting condition groups, one-way ANOVA was used. p values <0.05 were considered statistically significant. To examine epoch-by-epoch differences, t tests were conducted followed by post hoc Bonferroni corrections to correct for multiplicity.

RESULTS

Body Mass and Circadian Locomotor Rhythms

There was no interaction of lighting condition and body mass at any time point throughout the study (repeated measures, $p = 0.773$) or in final body mass (DLAN mean = 36.45 g, LD mean = 37.8 g; $p = 0.155$). Furthermore, both groups displayed normal 24-h circadian rhythms in running wheel activity, and had similar total activity levels as measured by mean wheel rotations per minute ($p = 0.496$), total wheel rotations ($p = 0.532$), number of rotations during the dark phase ($p = 0.570$), number of rotations during the light phase ($p = 0.641$), and percent of total rotations during the light phase ($p = 0.425$). See Figure 1 for more details.

Sleep Architecture and Homeostasis

No differences were observed between groups in total percent of time spent in the wake vigilance state across the 24-h recording period ($p = 0.829$) or within the light ($p = 0.108$) or dark ($p = 0.230$) phase when analyzed separately. Similarly there were no differences between groups in total percent of time spent in SWS across the 24-h recording period ($p = 0.970$) or within the light ($p = 0.145$) or dark ($p = 0.194$) phase. The mice did not display differences in total percent of time spent in REM sleep across the 24-h period ($p = 0.683$) or within the light ($p = 0.524$) or dark ($p = 0.879$) phase (Figure 2).

Furthermore, there were no differences between groups in total number of wake ($p = 0.203$), SWS ($p = 0.215$), or REM ($p = 0.392$) episodes. Groups were similar in maximum episode durations of wake ($p = 0.746$), SWS ($p = 0.761$), and REM sleep ($p = 0.683$), as well as average episode durations of wake ($p = 0.865$), SWS ($p = 0.834$), and REM sleep ($p = 0.956$).

Repeated-measures analysis of variance was conducted to examine differences within and between groups across epochs. Only REM sleep showed a significant interaction of lighting condition and time within subjects ($p = 0.003$), indicating the distribution (but not total amount) of REM was different between groups (Figure 3). This was evident in only the light phase ($p = 0.006$) when light and dark periods were analyzed separately. Furthermore, mean number of REM episodes ($p = 0.006$) and mean REM episode duration ($p = 0.043$) were influenced by the light condition × epoch interaction. This again was only evident in the light phase (REM mean episode number, $p = 0.016$; REM mean episode duration, $p = 0.033$) when light and dark periods were analyzed separately.

SWS mean episode number ($p = 0.016$) and wake mean episode number ($p = 0.016$) varied within subjects across the 24-h period. Only wake episode number differences remained significant ($p = 0.043$) in the dark phase when light and dark phases were analyzed separately.

In order to determine differences in sleep drive between groups, the delta power of SWS was examined (Figure 4). Delta power density values were not different across 24 h ($p = 0.801$), within the light phase ($p = 0.913$), or within the dark phase ($p = 0.222$). Delta power means also showed no interaction with lighting condition ($p = 0.207$) (Figure 4).

Body Mass and Sleep

Although light condition did not influence body mass in our sample, significant associations between body mass and amount of time spent in each vigilance state were evident (Figure 5A–C). Body mass was negatively correlated with percent of time spent in the wake vigilance state ($R = -0.780$, $p < 0.001$) and positively

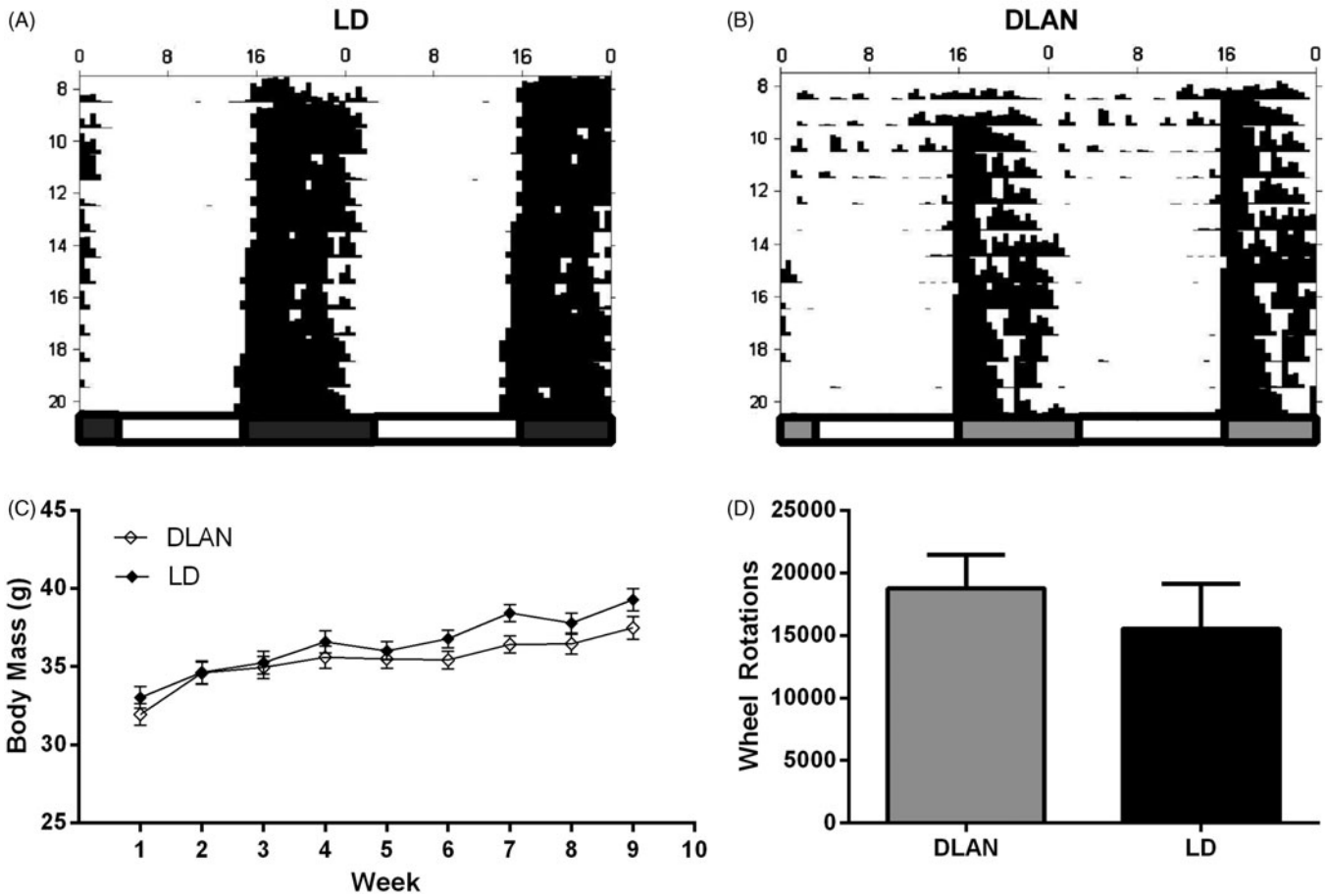

FIGURE 1. Dim light at night does not alter locomotor activity rhythms or body mass. (A) Actogram of a mouse housed in LD conditions. (B) Actogram of a mouse housed in DLAN conditions. (C) Mice body masses over the course of the study ($p = 0.773$). $n = 10$ per group. (D) Total number of wheel rotations over the course of the study ($p = 0.532$) (error bars represent SEM). $n = 10$ LD, 8 DLAN.

correlated with percent of time spent in SWS ($R = 0.767$, $p < 0.001$), but was not associated with percent of time spent in REM sleep ($R = 0.031$, $p = 0.909$).

Body mass did not correlate with amount of locomotor activity as measured by average wheel rotations per minute ($p = 0.332$), total wheel rotations ($p = 0.401$), rotations during the light ($p = 0.918$) or dark ($p = 0.209$) phase, or percent of rotations in the light phase ($p = 0.358$). Locomotor activity (as measured by total number of wheel rotations) did not correlate with percent of time spent in wake ($p = 0.891$), SWS ($p = 0.533$), or REM ($p = 0.065$) vigilance states. Body mass did not show any associations between measures of sleep fragmentation (REM sleep, SWS, and wake episode number and average duration, and REM sleep and SWS maximum episode duration) across either group or when grouped together. The exception to this rule was for maximum episode duration of the wake vigilance state, where animals that exhibited longer maximum episodes of sustained wakefulness (less fragmented) displayed lower mean body weights (in LD: $R = -0.770$, $p = 0.025$; in DLAN: $R = -0.751$, $p = 0.032$; groups combined: $R = -0.736$, $p = 0.001$) (Figure 5D).

DISCUSSION

DLAN and Sleep

The most parsimonious interpretation of our data is a failure to reject the null hypothesis; that is, sleep is not significantly affected by chronic exposure to dim light at night. No differences between groups were found in the primary measures of sleep quality or sleep architecture across the 24-h recording period or within the light or dark phase separately. However, repeated-measures analysis revealed that DLAN animals increase REM sleep at specific time points near the dark/light transition (Figure 3). This difference may reflect an influence of chronic DLAN exposure on the organization of REM sleep. Regardless, these mice still display the same total amount of REM sleep, REM episode number and duration, and delta power intensity as their dark night counterparts. These data indicate that, in mice, DLAN exposure likely influences immune, metabolic, and affective phenotypes independent of the homeostatic sleep system.

Intrinsically photosensitive retinal ganglion cells (ipRGCs) are non–image-forming cells of the retina that depolarize in response to light and (among other

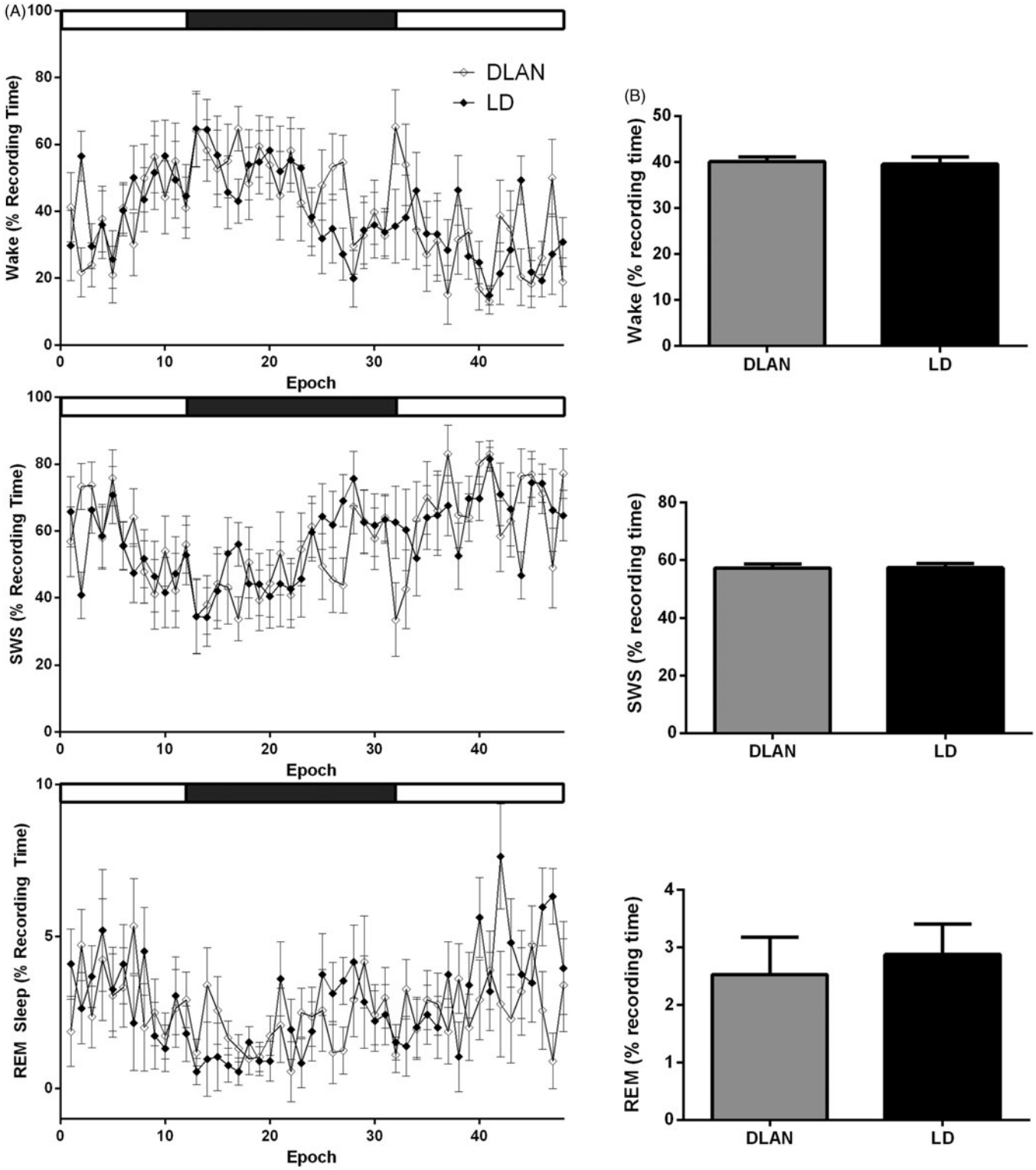

FIGURE 2. Dim light at night does not alter sleep architecture. (A) Wake, SWS, and REM sleep plotted as percent of the recording time across 24 h. Each point represents the mean value for the 30-min epoch. (B) Total mean values for wake ($p = 0.829$), SWS ($p = 0.970$), and REM sleep ($p = 0.683$) over 24 h (error bars represent SEM). $n = 8$ per group.

functions) transduce circadian signals to the suprachiasmatic nucleus of the hypothalamus. Inputs from these cells entrain endogenous clocks to external light cues and day/night cycles (Berson et al., 2002). These cells provide a pathway for non–image-forming light information to influence the circadian system without disrupting sleep homeostasis. ipRGCs are most sensitive to short-wavelength (~480 nm/blue) or full-spectrum (white) light (Mawad & Van Gelder, 2008), and are reliably depolarized at low light intensities (Berson, 2003).

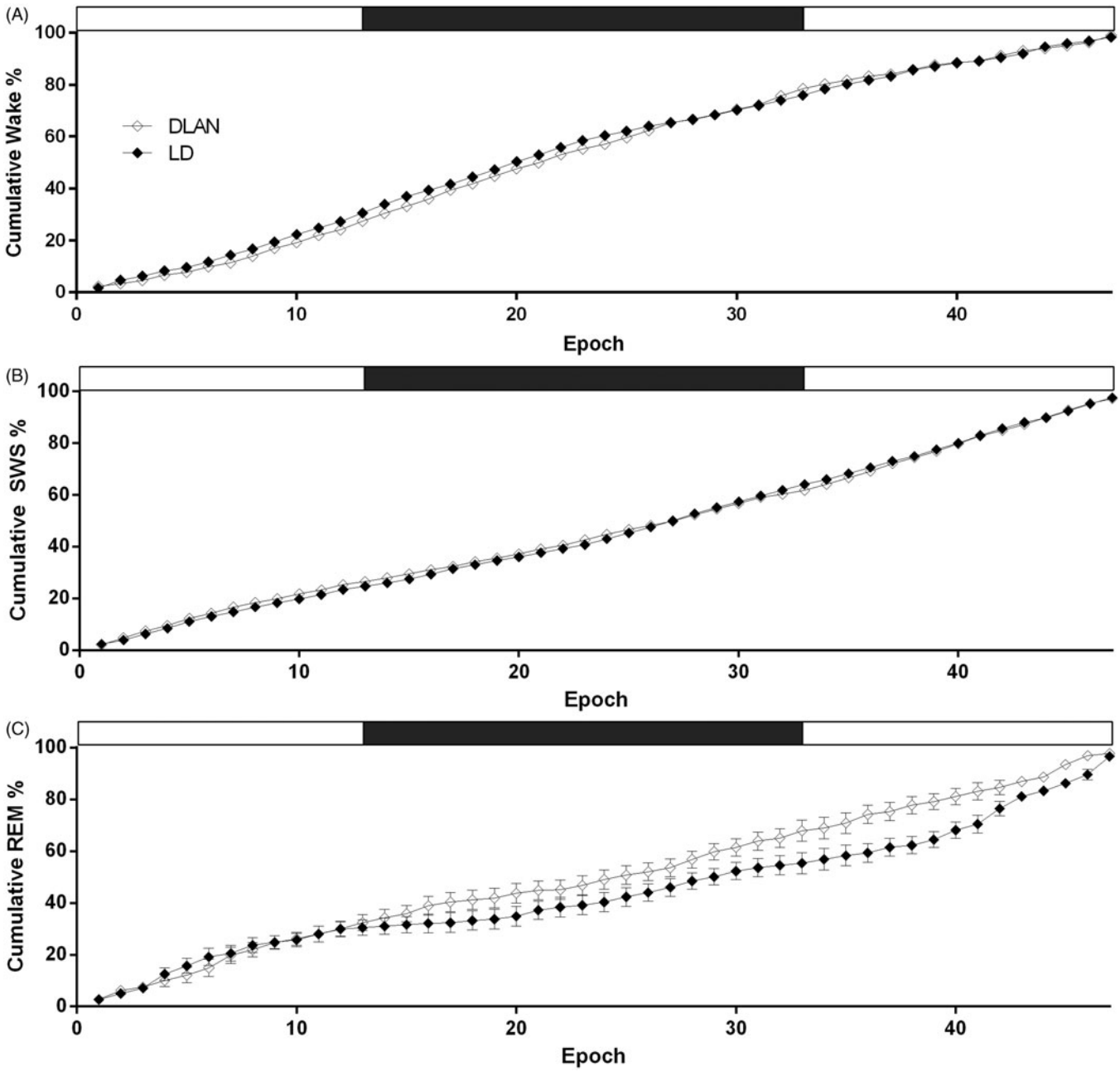

FIGURE 3. Dim light at night influences the distribution of REM sleep across the dark/light transition. Cumulative percentages for (A) wake, (B) SWS, and (C) REM sleep across the 24-h recording period. Each value represents the percent of time spent in each vigilance state added to the proceeding value (creating a cumulative % value). DLAN mice completed more of their REM sleep closer to the dark/light transition than the LD mice (repeated measures, $p = 0.006$). $n = 8$ per group.

Therefore, DLAN exposure likely affects immune, metabolic, and affective phenotypes through the action of ipRGCs on photic entrainment independent of sleep.

Body Mass and Sleep

Body masses did not differ between groups at any time point or upon final weigh in (Figure 1). Our previous studies have shown that mice maintained in DLAN conditions develop overweight phenotypes and glucose intolerance (Fonken et al., 2010). A likely explanation of this disparity in results is that in our previous studies, activity levels were monitored via intersecting infrared beams, and the mice were not given the opportunity to voluntarily exercise. We suggest that the effect of exercise (due to daily wheel running) contributed to the lack of group differences in body mass. Even though body mass did not correlate with wheel-running activity levels, all animals ran to some degree daily, and this was likely sufficient to eliminate the effects of DLAN on weight gain. However, it remains a possibility that DLAN affects sleep specifically in exercise-restricted mice, and this may have contributed to the increased body mass observed in previous studies.

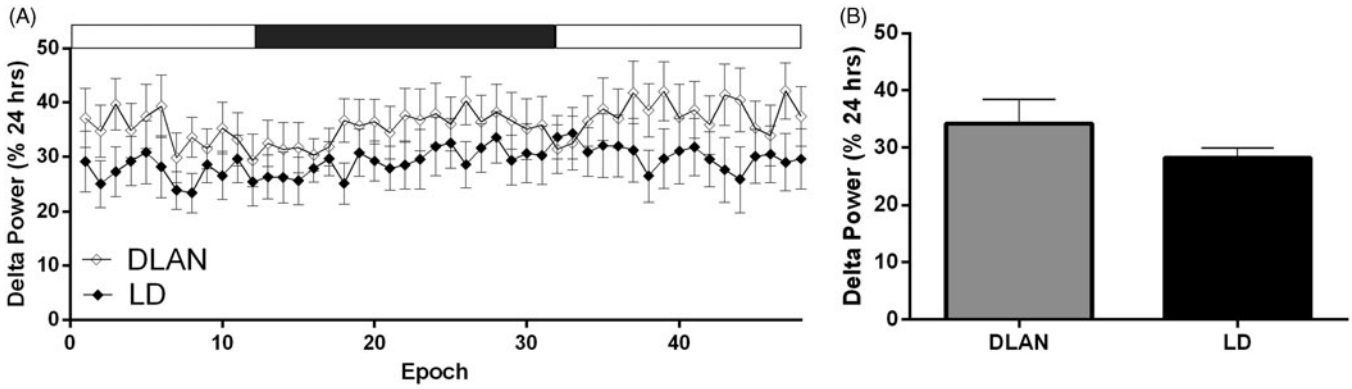

FIGURE 4. Dim light at night does not alter sleep drive. (A) Delta power as a relative percent of the 24-h recording period over time. Each point represents the mean value for the 30-min epoch ($p = 0.801$). (B) Total delta power means across the entire 24-h recording period ($p = 0.207$) (error bars represent SEM). $n = 8$ per group.

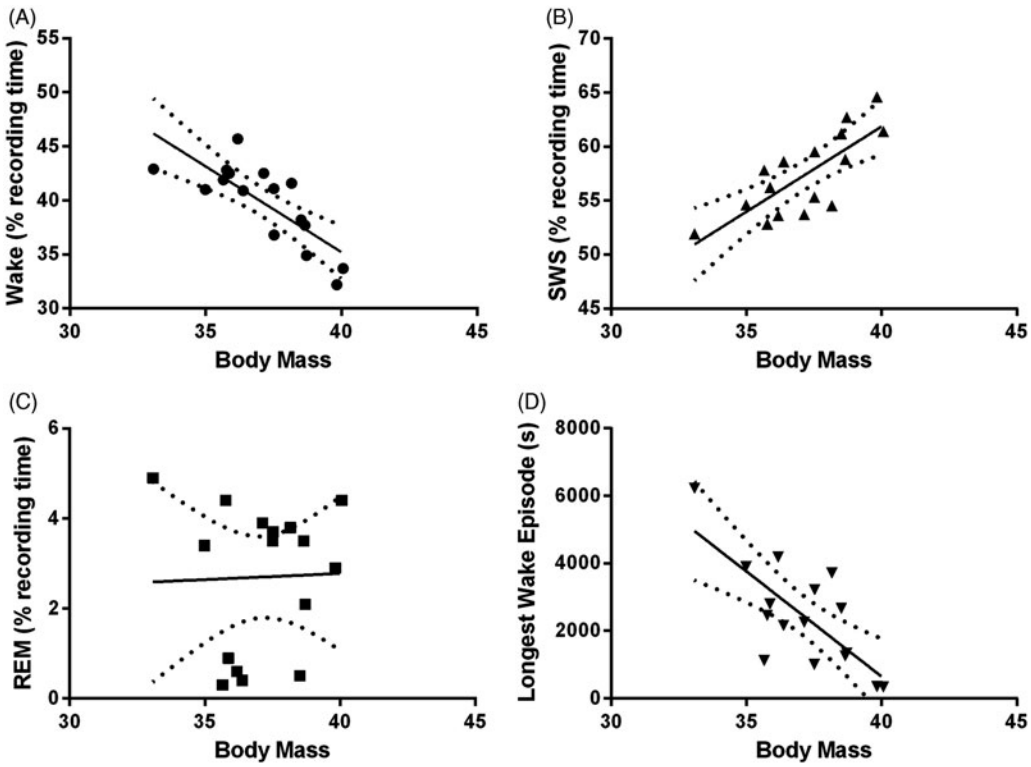

FIGURE 5. Body mass is associated with sleep quality and duration. (A) Body mass is negatively correlated with percent of the 24-h recording period spent in the wake vigilance state ($R = -0.780$, $p < 0.001$) and (B) is positively correlated with percent of time spent in SWS ($R = 0.767$, $p < 0.001$). (C) No relationship is evident between body mass and amount of time spent in REM sleep ($R = 0.031$, $p = 0.909$). (D) Body mass is negatively correlated with maximum duration of sustained wakefulness ($R = -0.736$, $p = 0.001$).

Body mass showed a strong relationship with percent of time spent in SWS and the wake vigilance state (Figure 5A–B). An obese mouse model of leptin deficiency (*ob/ob*) displays a similar increase in sleep time and decreased wake time (Laposky et al., 2005). The authors suggest that this is likely a compensatory mechanism due to increased sleep fragmentation, or effects of hormonal alterations due to leptin deficiency, rather than a cause of the obese phenotype. Similarly, obesity-resistant rats display elevated wake time and decreased time in SWS over a 24-h period (Mavanji et al., 2010). Obesity induced in mice by high-fat diet decreases wakefulness and increases SWS (but not REM sleep) (Jenkins et al., 2006). LD and DLAN mice did not display differences in sleep episode durations or number of episodes, indicating similar sleep quality. However, body mass was associated with maximum duration of sustained wake episodes (Figure 5D). This indicates that heavier animals had trouble maintaining longer bouts of wakefulness than their leaner counterparts, and thus experienced more fragmented periods of wakefulness. Our study suggests that body mass is directly related to amount of sleep, and indirectly related to amount of wakefulness in mice.

Furthermore, these relationships are evident in non–genetically modified mice fed normal chow (Harlan Teklad no. 8640; 17% kcal fat, 54% kcal carbohydrate, 29% kcal protein). These results are similar to previous reports in nocturnal rodents and humans, where obesity is related to elevated sleep duration, reduced wake duration, and the fragmentation of sleep/wake states (reviewed in Maravanji et al., 2012).

CONCLUSION

Our results indicate that (1) chronic DLAN exposure does not significantly influence sleep architecture or homeostasis and (2) normally distributed body masses show marked relationships to amount of time in wake and SWS vigilance states, as well as to maximum time spent in sustained wakefulness. These data lend support to previous results suggesting a sleep-independent mechanism of DLAN on metabolic, immune, and affective phenotypes. Therefore, researchers interested in the chronodisruptive effects of chronic light exposure should consider using DLAN to control for sleep disturbances in future research.

ACKNOWLEDGMENTS

We would like to thank the University Laboratory Animal Resources staff at Ohio State University for providing excellent care of the animals used in this study.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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