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Exercise attenuates the metabolic effects of dim light at night

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HIGHLIGHTS

- Mice exposed to dim, rather than dark nights, increase body mass gain.
- Access to a running wheel prevents weight gain in mice exposed to dimly lit nights.
- Exposure to dim light at night or access to a running wheel increases daytime food intake.
- Dim light at night disrupts the 24 h rhythm in wheel running in a subset of mice.
- Exercise limits weight gain in dLAN mice without rescuing circadian alterations.

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ABSTRACT

Most organisms display circadian rhythms that coordinate complex physiological and behavioral processes to optimize energy acquisition, storage, and expenditure. Disruptions to the circadian system with environmental manipulations such as nighttime light exposure alter metabolic energy homeostasis. Exercise is known to strengthen circadian rhythms and to prevent weight gain. Therefore, we hypothesized providing mice a running wheel for voluntary exercise would buffer against the effects of light at night (LAN) on weight gain. Mice were maintained in either dark (LD) or dim (dLAN) nights and provided either a running wheel or a locked wheel. Mice exposed to dim, rather than dark, nights increased weight gain. Access to a functional running wheel prevented body mass gain in mice exposed to dLAN. Voluntary exercise appeared to limit weight gain independently of rescuing changes to the circadian system caused by dLAN; increases in daytime food intake induced by dLAN were not diminished by increased voluntary exercise. Furthermore, although all of the LD mice displayed a 24 h rhythm in wheel running, nearly half (4 out of 9) of the dLAN mice did not display a dominant 24 h rhythm in wheel running. These results indicate that voluntary exercise can prevent weight gain induced by dLAN without rescuing circadian rhythm disruptions.

1. Introduction

Over the course of the 20th century body mass rapidly increased worldwide. By the year 2000 the number of adults with excess weight surpassed those who were underweight for the first time in human history. This excess adiposity is recognized as one of the world's leading health threats because obesity increases the risk of developing type II diabetes, cardiovascular disease, hypertension, and cancer [7]. The rapid growth in adiposity during the 20th century correlates with significant changes in human environment and lifestyle. In addition to changes in activity levels and dietary choices, a less appreciated environmental perturbation has been the shift in timing of daily activities. The invention of electrical lighting ~150 years ago has enabled humans to illuminate their homes, hospitals, factories, and night skies and engage in activities such as countercyclical shift work [23]. Widespread adoption of electric lights occurred well before an understanding of circadian biology, and without any consideration of the negative biological consequences that artificial light at night (LAN) may have on physiology and behavior.

Circadian regulation of energy homeostasis is organized by an endogenous biological clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus. The circadian clock is entrained by light information that travels directly from light-sensitive ganglion cells in the retina to the SCN, thereby synchronizing individuals' physiology and behavior to the external day–night cycle [16,30]. Because light is the primary signal for the circadian clock, exposure to light at aberrant times can disrupt clock function [23].

Many studies suggest a direct link between the molecular circadian clock and metabolism [6]. Mice harboring a mutation in the core circadian gene *Clock* are susceptible to obesity and metabolic syndrome [33]. *Clock* mutants show dramatic changes in circadian rhythmicity, as well

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as altered timing of food intake and increased body mass. Serum leptin, glucose, cholesterol, and triglyceride levels are increased in *Clock* mutants compared to wild type (WT) mice. Mice with mutations in other clock related genes including *Bmal1*, *Per1*, *Per2*, *Vipr2*, and *Rev-erbα* display similar metabolic outcomes [3,8,10,19]. Even single tissue clock gene disruptions can result in metabolic disturbances [19,26]. Thus, it seems reasonable to propose that disrupted circadian clock function has the potential to derange normal metabolism.

Mice housed in dim LAN (dLAN) elevate body mass and reduce glucose tolerance independent of changes in total daily food intake or home cage locomotor activity (Fonken et al., 2010). dLAN mice increase the percentage of food consumed during the light phase as compared to mice housed in dark nights; restricting food intake to the dark phase ameliorates weight gain among dLAN mice (Fonken et al., 2010). Daytime food intake is associated with weight gain and metabolic disruption in mice in other contexts [1,5]. Furthermore, the relationship between the circadian clock and metabolism appears to be bidirectional as diet induced obesity can dampen circadian rhythms [18].

As mentioned, light is the dominant entraining factor for the circadian system; however, non-photic stimuli such as food intake and exercise can alter circadian rhythms [15,21]. Activity is both a behavioral output of the circadian system and an important feedback factor that can modulate rhythms [11,20,29]. In constant dark conditions, timed wheel access entrains circadian rhythms in mice [11]. Moreover, scheduled access to a running wheel can strengthen circadian rhythms in mice with disrupted clock function [28]. Even under a standard light–dark cycle, ad lib access to wheels can strengthen the power of circadian rhythms in wild type mice [31].

In addition to strengthening circadian rhythms, it is well established that exercise prevents weight gain [27]. Therefore, we hypothesized providing mice a running wheel for voluntary exercise would buffer against the effects of LAN on metabolism. Specifically, we hypothesized that mice exposed to LAN would increase body mass and alter feeding rhythms, indicating circadian system disruption. We predicted that providing mice running wheels would strengthen circadian entrainment preventing altered timing of food intake and LAN-induced weight gain.

2. Materials and methods

2.1. Animals

Forty male Swiss-Webster mice (~8 weeks of age) were obtained from Charles River Laboratories. The mice were individually housed in propylene cages (dimensions: 33 × 19 × 14 cm) at an ambient temperature of 22 ± 2°C and provided with Harlan Teklad 8640 food (Madison, WI) and filtered tap water ad libitum. Upon arrival, mice were maintained in a standard 14:10 light (150 lx)/dark (0 lx) cycle (LD; lights on at 2:00 EST) for 1 week in order to habituate to local lighting conditions and recover from the effects of shipping. After this period mice were randomly assigned a group, weighed, and transferred to either a cabinet with LD or dim light at night [dLAN; 14:10 light (150 lx)/dim (5 lx) light cycle]. Within each lighting condition mice received either a locked wheel or a low-profile running wheel (running surface of 15.5 cm diameter) for voluntary exercise (Med Associates, St. Albans, VT). Wheel running was constantly monitored using a wireless interface hub system which transmitted the data to a computer. Locked wheels were provided to control for the presence of a novel object in the cage. Mice were weighed every week at Zeitgeber Time (ZT) 7.

After 3 weeks in experimental conditions, food was weighed twice daily, immediately before the onset of the dark phase (ZT 12) and immediately after the onset of the light phase (ZT 22). Average food intake for the light and dark phases over three days was used to quantify percentage of daytime food intake. At the conclusion of the study mice were individually brought into a procedure room, anesthetized with isoflurane vapors, and rapidly decapitated between ZT 7 and 9; a blood sample was then collected and epididymal fat pads were removed and weighed.

2.2. Statistical analyses

One dLAN mouse with a running wheel was removed from statistical comparisons because it did not use the wheel and one mouse was removed from the locked wheel LD group for demonstrating sickness behaviors. Effects of lighting condition and wheel access on body mass gain,

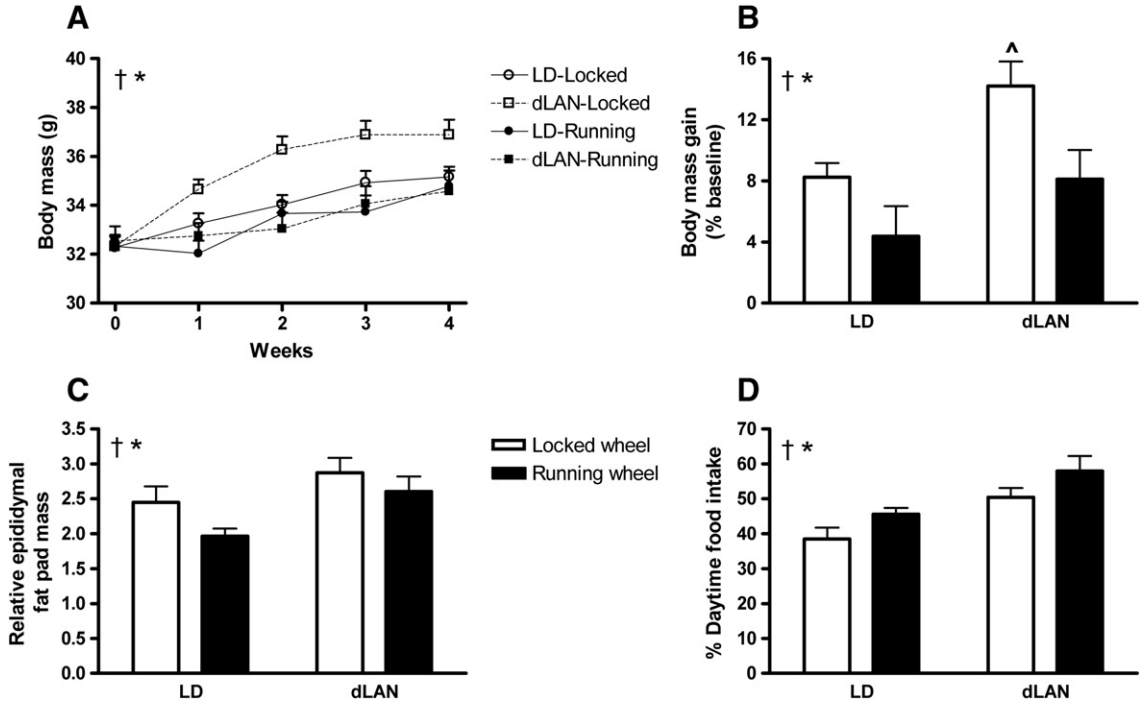

Fig. 1. Voluntary exercise prevents weight gain induced by exposure to dLAN. (A) Body mass over the course of the study. (B) Body mass gain expressed relative to baseline body mass. (C) Epididymal fat pad mass expressed relative to final body mass. (D) Percentage of food consumed during the light phase. All data are presented as mean ± SEM. *indicates main effect of lighting condition, †indicates main effect of wheel, ^differs from all other groups.

fat pad mass, and percentage of daytime food intake were analyzed using two-way analysis of variance (ANOVA). A repeated measures ANOVA was used to assess change in body mass over time. Following a significant F score, multiple comparisons were conducted with Tukey's HSD test. The above statistical analyses were performed with StatView software (v.5.0.1, Cary, NC). Running wheel activity was analyzed and actograms were generated using ClockLab Software (Coulbourn Instruments, Boston, MA). An animal was considered rhythmic when the highest peak occurred at ~1 cycle/24 h, with an absolute power of at least 0.005 mV/Hz (Kriegsfeld, et al., 2008). In all cases, differences between group means were considered statistically significant if $p \leq 0.05$.

3. Results

3.1. Somatic measures

Over the course of the study, body mass was elevated among all groups ($F_{4,136} = 82.814$; $p < 0.0001$); however, light at night potentiated increases in body mass, whereas access to a running wheel limited weight gain (Body mass over time: $F_{4,136} = 4.275$ and 4.659 respectively, Final body mass gain: $F_{1,\ 34} = 7.711$ and 8.203 respectively; $p < 0.01$; Fig. 1A/B). Final body mass gain did not differ between mice exposed to dLAN with a running wheel and mice housed in dark nights with either a running or locked wheel (*post hoc*; $p < 0.05$). There were no interactions of the two variables on weight gain. Both light and access to a running wheel also affected final fat pad mass ($F_{1,33} = 7.505$ and 3.791; Fig. 1C); such that dLAN increased fat pad mass and presence of a running wheel reduced fat pad mass. In agreement with previous results, mice housed in dLAN increased percentage of food consumed during the light phase ($F_{1,34} = 14.345$; $p < 0.001$; Fig. 1D). In contrast to our hypothesis, wheel running also increased the percentage of food consumed during the light phase ($F_{1,34} = 5.265$; $p < 0.05$; Fig. 1D).

3.2. Daily running wheel activity

Total daily wheel running did not differ between mice in the LD and dLAN conditions ($F_{1,17} = 0.144$; $p > 0.1$; data not shown). All mice in LD showed a dominant rhythm of 0.042 (or 1 cycle per 24 h) (Fig. 2A). In contrast, only 5 of the 9 dLAN-mice demonstrated a dominant 24 h wheel running rhythm (Fig. 1B).

4. Discussion

The goal of this study was to assess the effects of voluntary exercise on changes in body mass and food intake associated with exposure to dLAN in male Swiss Webster mice. We hypothesized that enhanced activity by means of optional wheel running would prevent body mass gain in mice exposed to dLAN. Specifically, we predicted that voluntary exercise would

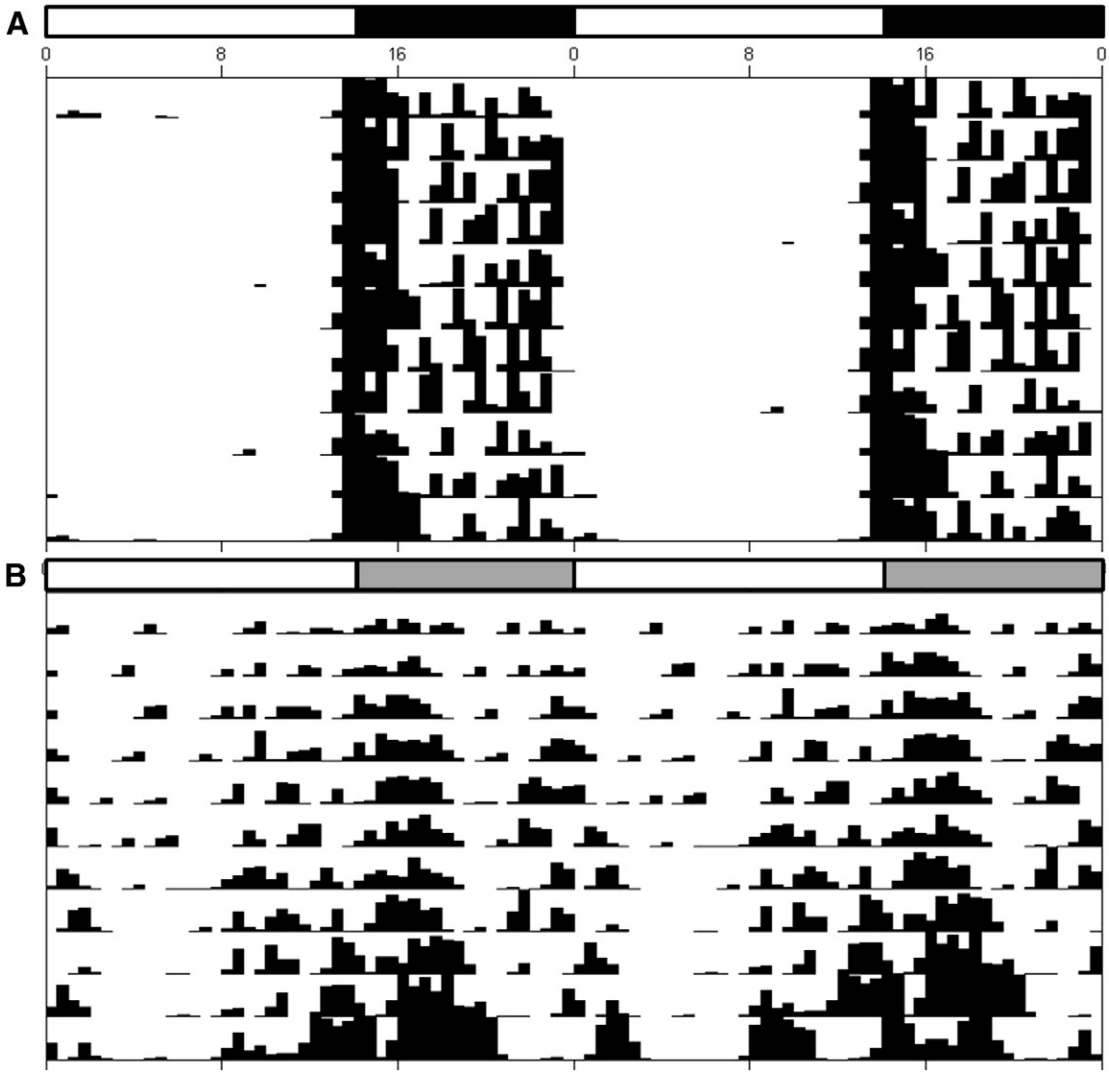

Fig. 2. Representative actrograph from a mouse housed in either (A) dark or (B) dim nights.

strengthen circadian organization in mice exposed to dLAN, preventing increased daytime food intake. Here we show, exercise availability limits weight gain in mice housed under dLAN. In contrast to our hypothesis, reduced body mass occurred independently of re-establishing nighttime food intake; mice with running wheel access increased food intake during the light phase. Furthermore, although all mice maintained under dark nights had a dominant 24 h activity rhythm, a subset of the dLAN mice showed disrupted patterns of wheel running.

Our results confirm and extend previous findings [9,13,14]; mice exposed to LAN without access to wheel running elevated body mass gain over the course of the study. Consistent with our hypothesis, access to a running wheel reduced weight gain among mice exposed to dLAN. Final body mass gain was comparable between dLAN mice with a running wheel and both groups of LD mice. Furthermore, whereas dLAN increased relative epididymal fat pad mass, an index of overall adiposity, housing mice with a running wheel reduced fat pad mass. These results indicate that weight gain induced by dLAN is susceptible to traditional weight loss interventions, i.e. increased exercise.

As in previous studies, dLAN mice ate more food during the light phase compared to mice exposed to dark nights [14]. Eating during the light part of the day is atypical for nocturnal rodents and is associated with changes in metabolism [1,5]. Moreover, restricting food intake to the dark phase prevents weight gain in models of obesity [14,17,22,32]. Voluntary wheel running has previously been associated with increasing the power of ambulatory activity rhythms with greater activity specifically during the dark phase in mice housed in standard lighting conditions [31]. Thus, we predicted that access to a running wheel would prevent the shift towards daytime food intake in dLAN mice. Contrary to our prediction, presence of a running wheel increased daytime food intake irrespective of lighting condition. These results differ from rats; rats with either voluntary wheel running or forced exercise consume more calories during the active phase [25]. To our knowledge the effects of voluntary wheel running on the daily pattern of food intake in mice has not been investigated. However, mice with access to running wheels have fewer, but larger, daily meals [2].

Total daily wheel running did not differ between mice exposed to dark or dimly illuminated nights. These findings are consistent with previous research demonstrating that exposure to dLAN does not affect the amount of activity in either an open field or home cage [12,14]. Circadian rhythms of home cage locomotor activity remain intact in mice exposed to dLAN and comparable to activity patterns in mice exposed to dark nights (Fonken et al., 2010). In the present study, however, wheel running activity was disrupted in several dLAN mice. All mice exposed to dark nights displayed a dominant 24 h rhythm in wheel running compared to 5 of 9 mice exposed to dLAN. Although we have previously asserted that dLAN does not affect sleep architecture or activity patterns [4], these results indicate that dim light may shift circadian activity when paired with optional wheel running. Future studies should address sleep quantity and quality in mice exposed to LAN. Disparate results between wheel running and home cage activity could reflect the different forms of behavior that the two systems monitor [24]. Home cage activity occurs for multiple reasons including grooming, feeding, or locomotor activity, whereas running wheels only monitor voluntary running. Overall, these results suggest that voluntary exercise prevents weight gain induced by dLAN without rescuing circadian rhythm disruptions.

Conflicts of interest statement

The authors declare no conflicts of interest.

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