

ORIGINAL ARTICLE

Acute dim light at night increases body mass, alters metabolism, and shifts core body temperature circadian rhythms

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The circadian system is primarily entrained by the ambient light environment and is fundamentally linked to metabolism. Mounting evidence suggests a causal relationship among aberrant light exposure, shift work, and metabolic disease. Previous research has demonstrated deleterious metabolic phenotypes elicited by chronic (>4 weeks) exposure to dim light at night (DLAN) (~5 lux). However, the metabolic effects of short-term (<2 weeks) exposure to DLAN are unspecified. We hypothesized that metabolic alterations would arise in response to just 2 weeks of DLAN. Specifically, we predicted that mice exposed to dim light would gain more body mass, alter whole body metabolism, and display altered body temperature (T_b) and activity rhythms compared to mice maintained in dark nights. Our data largely support these predictions; DLAN mice gained significantly more mass, reduced whole body energy expenditure, increased carbohydrate over fat oxidation, and altered temperature circadian rhythms. Importantly, these alterations occurred despite similar activity locomotor levels (and rhythms) and total food intake between groups. Peripheral clocks are potently entrained by body temperature rhythms, and the deregulation of body temperature we observed may contribute to metabolic problems due to “internal desynchrony” between the central circadian oscillator and temperature sensitive peripheral clocks. We conclude that even relatively short-term exposure to low levels of nighttime light can influence metabolism to increase mass gain.

Keywords: Body temperature, calorimetry, circadian, metabolism, light at night

INTRODUCTION

Metabolism and circadian rhythms are fundamentally linked; alterations to one system elicits changes in the other (Bass & Takahashi, 2010; Eckel-Mahan & Sassone-Corsi, 2013; Rutter et al., 2002; Solt et al., 2012). The circadian system is primarily entrained by the ambient light environment, coupled to the day/night cycle to regulate behavior and physiology in a temporally appropriate manner (Albrecht et al., 1997; Do & Yau, 2010; Shigeyoshi et al., 1997).

Within the past century, artificial light exposure has become commonplace throughout the developed world, with ~99% of the US and European populations experiencing significant night-time illumination (Cinzano et al., 2001; Fonken & Nelson, 2011; Navara & Nelson, 2007). However, humans and other animals have not evolved in this ecological context. This raises the possibility that aberrant light exposure may influence metabolism by altering the circadian system (Wyse et al., 2011).

Previous research has demonstrated the deleterious effects of chronic (>4 weeks) dim light at night (DLAN) exposure in both nocturnal (e.g. Bedrosian et al., 2012; Fonken et al., 2013a; Shuboni & Yan, 2010) and diurnal rodents (e.g. Fonken et al., 2012). Specifically, chronic DLAN exposure increases body mass without altering total food consumption or activity levels by shifting the timing of food intake (Fonken et al., 2010). This phenomenon is likely not driven by sleep disruption; neither sleep timing nor sleep quality is affected by DLAN in mice (Borniger et al., 2013). As peripheral oscillators in hepatic and adipose tissues are entrainable by food (Menaker et al., 2013), the increase in body mass may be due to “internal desynchrony” between central and peripheral clocks controlling metabolism. Indeed, DLAN alters the expression rhythms of several core clock genes in the liver and adipose tissues (Fonken et al., 2013a), possibly contributing to mass gain.

Although chronic DLAN exposure reliably increases body mass, the “minimum dose” of DLAN required to

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promote metabolic abnormalities is undefined although preliminary evidence suggests that increases in body mass are evident as soon as 4 d after placement into dim light conditions (Fonken et al., 2013b). Furthermore, the circadian phenotype of body temperature (T_b) rhythms has not been investigated in the context of DLAN. We hypothesized that brief (<2 weeks) exposure to DLAN alters metabolism. We predicted that over the course of 2 weeks, DLAN animals would gain more mass and decrease energy expenditure as measured by indirect calorimetry. We also predicted that DLAN would alter circadian rhythmicity in core body temperature, as peripheral clocks are potently entrained by the daily body temperature rhythm (Brown et al., 2002; Saini et al., 2012), which contributes to the synchronization of the clock “network” to ensure optimal function (Menaker et al., 2013).

MATERIALS AND METHODS

Animals and light conditions

Adult (>9 weeks) male Swiss-Webster mice were singly housed in polypropylene cages (27.8 × 7.5 × 13 cm) with *ad libitum* food (Harlan-Taklad no. 8640; Harlan Laboratories, Indianapolis, IN) and water access on a 14:10 light/dark schedule for 2 weeks following arrival to our laboratory. Room temperature remained at 22 ± 2 °C for the duration of the study. Lights were illuminated from 0100 (ZT 0) to 1500 (ZT 14). After 2 weeks, mice underwent transmitter implantation surgery (see below), and were then returned to their home cages to recover for an additional 2 weeks prior to the start of the experiment.

After recovery and baseline metabolic measurements, mice were randomly assigned to either remain under dark night conditions (14 h light (~150 lux)/10 h dark (~0 lux)) or switched to DLAN conditions (14 h light (~150 lux)/10 h dim light (~5 lux)) in an adjacent room until the conclusion of the study. Dim light was supplied by a compact fluorescent lamp (Ecosmart, Inc; 9 Watt, 2700K “soft white”, 550 lumens) placed equidistant from all cages. A light meter was placed in each cage and light levels (lux) were measured prior to animal placement into the cage and adjusted to ensure ~5 lux exposure at eye level. This study was conducted with 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).

Transmitter implant

Following habituation to our facilities, mice were implanted intraperitoneally with radiotelemetric transmitters as described previously (Bedrosian et al., 2011) (G2 E-Mitter, Mini Mitter Company, Inc., Respironics Inc.; Bend, OR) under isoflurane anesthesia and allowed to recover for 1 week prior to initial baseline measures.

Body masses were corrected for the weight of the transmitter, and consideration was given to the effects of implantation on body mass regulation (Adams et al., 2001). Home cages were placed on top of TR-3000 receiver boards connected to a desktop computer running VitalView software (Mini-Mitter, Starr Life Sciences Corp., Pittsburgh, PA), which continuously collected activity and temperature data in 30 min bins.

Indirect calorimetry

Whole body metabolic measures were collected via the comprehensive laboratory animal monitoring system (CLAMS; Oxymax, Columbus Instruments, Columbus, OH) as described elsewhere (Warner et al., 2010). Briefly, at baseline and after 2 weeks in dim or dark night conditions, mice were placed into CLAMS metabolic chambers (10.4 × 8.6 × 20.2 cm) for 24 h. During one testing session, the recording computer malfunctioned at 0320 and data after that time point were lost. Therefore, to ensure adequate comparisons between sampling points, metabolic data were analyzed 2 h prior and 2 h after lights on to determine differences in metabolic output between groups across the Dark → Light transition. Food was weighed prior to entry into the chambers and then immediately after removal 24 h later to assess total food intake. Water was supplied *ad libitum*. Dim light exposure was maintained for the dim light group during the second metabolic session via white broad spectrum LEDs dimmed to ~5 lux at cage level as previously described (Bedrosian et al., 2013).

Volume O₂ (ml/h), volume CO₂ (ml/h), respiratory exchange ratio ((VCO₂/VO₂) RER), heat production (kcal/hr) (VO₂ × [3.815 + (1.232 × RER)]) and physical activity (*x* and *z* axis infra-red beam breaks) were assessed every 20 min for each animal. Animal masses were determined immediately prior to placement into the metabolic chambers, and this mass value was subsequently used as a covariate in metabolic analyses. Kleiber’s law or similar exponent rules were not used as these data modifications have been proven to be inappropriate and provide inaccurate results (Tschöp et al., 2012).

Data analysis

To determine circadian rhythms in T_b and activity, 30-min VitalView output files were transferred into LSP (Circadian Rhythm Laboratory, University of South Carolina, Walterboro, SC) and period (τ) was calculated by the Lomb-Scargle periodogram procedure. All animals displayed a circadian ($f = \sim 1/24$) T_b and activity rhythm. To assess if DLAN elicited an “uncoupling” of T_b and activity rhythms, the absolute value of the difference between their peak values after “lights off” was determined: (Unc = |HrPkAct – HrPkT_b|), where “Unc” is the absolute value of uncoupling (in hours) between body temperature and activity rhythms, “HrPkAct” is the

number of hours after “lights off” that activity peaked, and “HrP_kT_b” is the number of hours after “lights off” that T_b peaked.

Repeated measures analysis of variance (ANOVAs) were used to analyze body mass, metabolic measures, body temperature, and activity over time. Zeitgeber Time (ZT) was used as the within subjects variables, and light condition was used as the between subjects variable. If significant *F* values were detected, then single time point comparisons were conducted using general linear model univariate ANOVAs. When appropriate, mean values between groups were compared using one-way ANOVA. When analyzing metabolic outputs, time point specific body masses (baseline or week 2) were used as covariates. To assess changes in mean values within light condition groups over the course of 2 weeks, the baseline and week 2 values were compared using paired-samples *t*-tests split by light condition group. Mean differences were considered statistically significant when $p \leq 0.05$. Statistics were completed using SPSS Statistics version 21 (IBM, Armonk, NY) and visualized using GraphPad Prism 5 (GraphPad Software, San Diego, CA).

RESULTS

Body mass, food intake and activity

Mice exposed to DLAN gained substantially more mass than their dark night counterparts over the course of 2

weeks ($F_{1,15} = 20.58$, $p < 0.05$; Figure 1A). After 2 weeks, dim light animals weighed ~12% more than baseline values while dark night animals weighed ~5% more than at baseline ($F_{1,15} = 33.69$, $p < 0.05$; Figure 1B).

Baseline food intake did not differ between light condition groups ($F_{1,14} = 0.02$, $p > 0.05$; Figure 1C), or after 2 weeks of dim light exposure (Figure 1C) ($F_{1,15} = 0.76$, $p > 0.05$). Irrespective of light condition, both groups increased their total food intake between baseline and week 2 (LD: $t(7) = 3.74$, $p < 0.05$; DLAN: $t(7) = 4.675$, $p < 0.05$). Similarly, average activity levels did not differ between light condition groups at baseline ($F_{1,14} = 0.013$, $p > 0.05$; Figure 1D) or after 2 weeks ($F_{1,14} = 0.017$, $p > 0.05$). No differences in average locomotor activity were observed during the light ($F_{1,14} = 0.001$, $p > 0.05$) or dark ($F_{1,14} = 0.025$, $p > 0.05$) phases at baseline or after 2 weeks (light: $F_{1,14} = 0.484$, $p > 0.05$; dark: $F_{1,14} = 0.054$, $p > 0.05$).

Indirect calorimetry

Mice did not differ in the volume of oxygen (VO₂) consumed at baseline ($F_{1,15} = 2.01$, $p > 0.05$). However, at week 2, there was a significant effect of light condition on VO₂ ($F_{1,15} = 1.828$, $p < 0.05$), with dim light exposed animals using significantly less O₂ (Figure 2A). Similarly, at baseline, mice did not differ in the ratio of carbon dioxide production to oxygen consumption (RER) ($F_{1,15} = 1.46$, $p > 0.05$). At week 2, however, dim light exposed animals had significantly

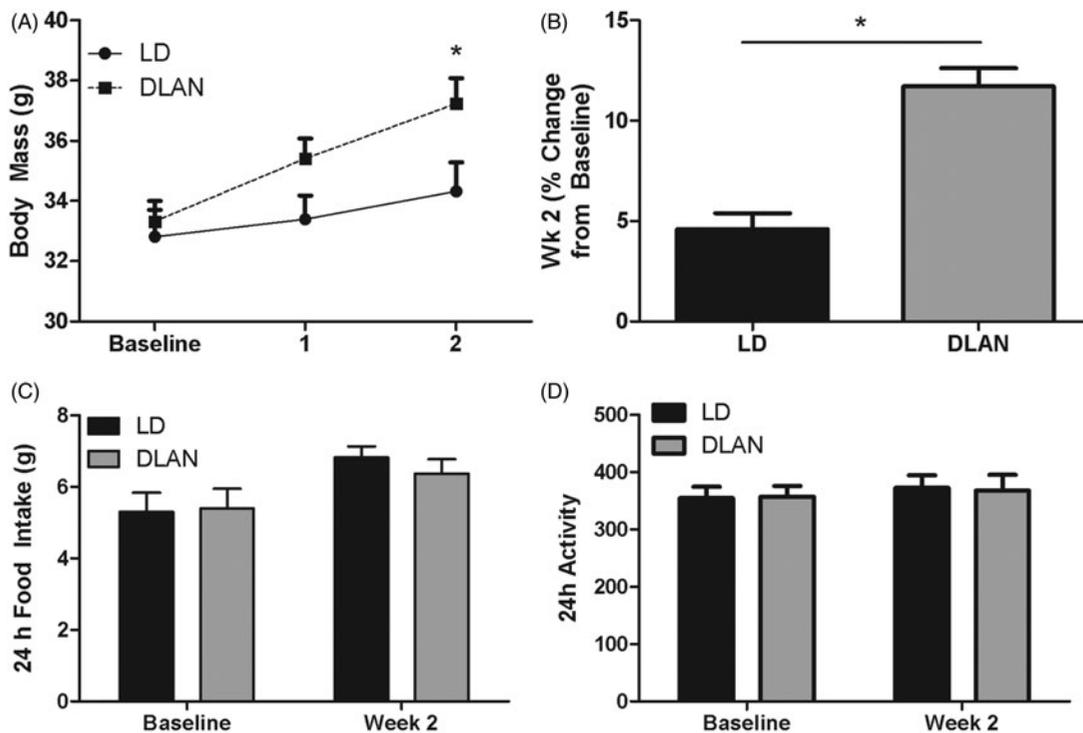


FIGURE 1. DLAN increases body mass within 2 weeks of exposure without altering total food intake or activity levels. (A) Body mass over time (B) % change in body mass from baseline values. (C) Total 24 h food intake and (D) average locomotor activity (minimitter) (Error bars represent SEM; $N = 8-9$ per group; $*p < 0.05$).

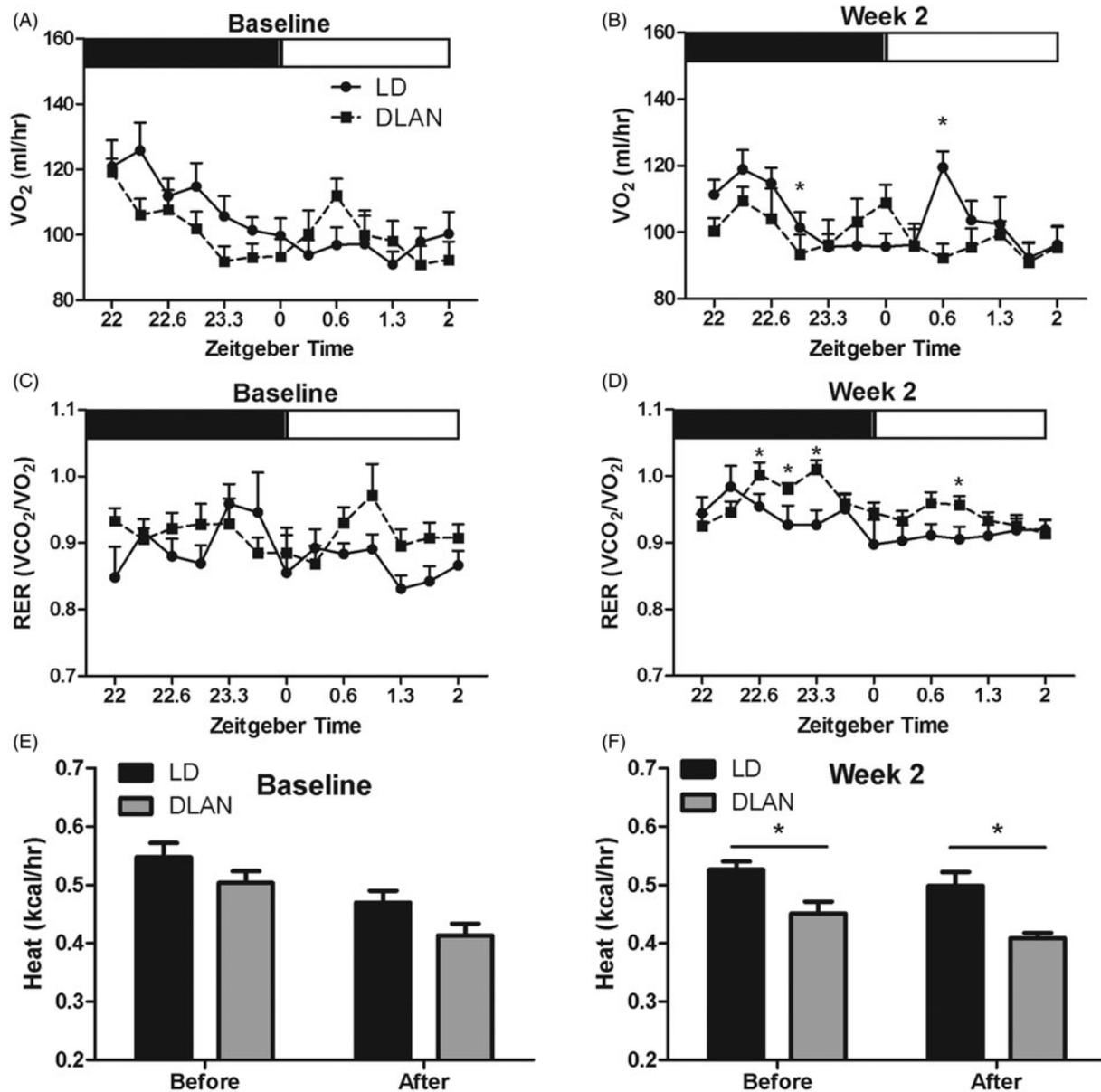


FIGURE 2. DLAN alters metabolic measures across the Dark→Light Transition. (A) VO_2 consumption 2 h prior and 2 h after lights on at baseline and (B) at week 2 and (C) RER at 2 h prior and 2 h after lights on at baseline and (D) at week 2. (E) Average Heat (kcal/h) production before lights on and after lights on at baseline and (F) at week 2. (Error bars represent SEM; $N=8-9$ per group; $*p < 0.05$).

higher RER values than their dark night counterparts ($F_{1,15} = 2.74$, $p = 0.05$) (Figure 2B), indicating a preference for carbohydrate over fat metabolism independent of protein oxidation. When energy expenditure (heat production) was analyzed across the Dark → Light transition, baseline values were similar between groups (Figure 2E) (Before Lights On: $F_{1,14} = 2.244$, $p > 0.05$; After Lights On: $F_{1,14} = 4.00$, $p > 0.05$). However, at week 2, DLAN animals significantly reduced energy expenditure both before ($F_{1,14} = 11.3$, $p < 0.05$) and after ($F_{1,14} = 16.06$, $p < 0.05$) lights on (Figure 2F).

Body temperature and activity rhythms

DLAN and dark night exposed animals displayed similar circadian rhythms in body temperature (T_b) at

baseline (Figure 3A, C). Period (τ) at baseline was equivalent between groups ($F_{1,14} = 2.5$, $p > 0.05$) and during the 2nd week of DLAN exposure ($F_{1,14} = 0.03$, $p > 0.05$) (Figure 3E), indicating that DLAN did not cause arrhythmic T_b over the 2-week exposure time. Repeated measures analysis of a single day of T_b at baseline and at day 10 revealed significant differences over the course of the day at week 2 ($F_{1,14} = 2.66$, $p < 0.05$), but not at baseline ($F_{1,14} = 0.79$, $p > 0.05$) (Figure 3C, D).

Upon examination of T_b across the dark and light phases, DLAN reduced the normal dark/light phase difference in T_b at week 2 ($F_{1,14} = 15.35$, $p < 0.05$), but were equivalent at baseline ($F_{1,14} = 1.51$, $p > 0.05$) (Figure 3F). Furthermore, the dark/light phase

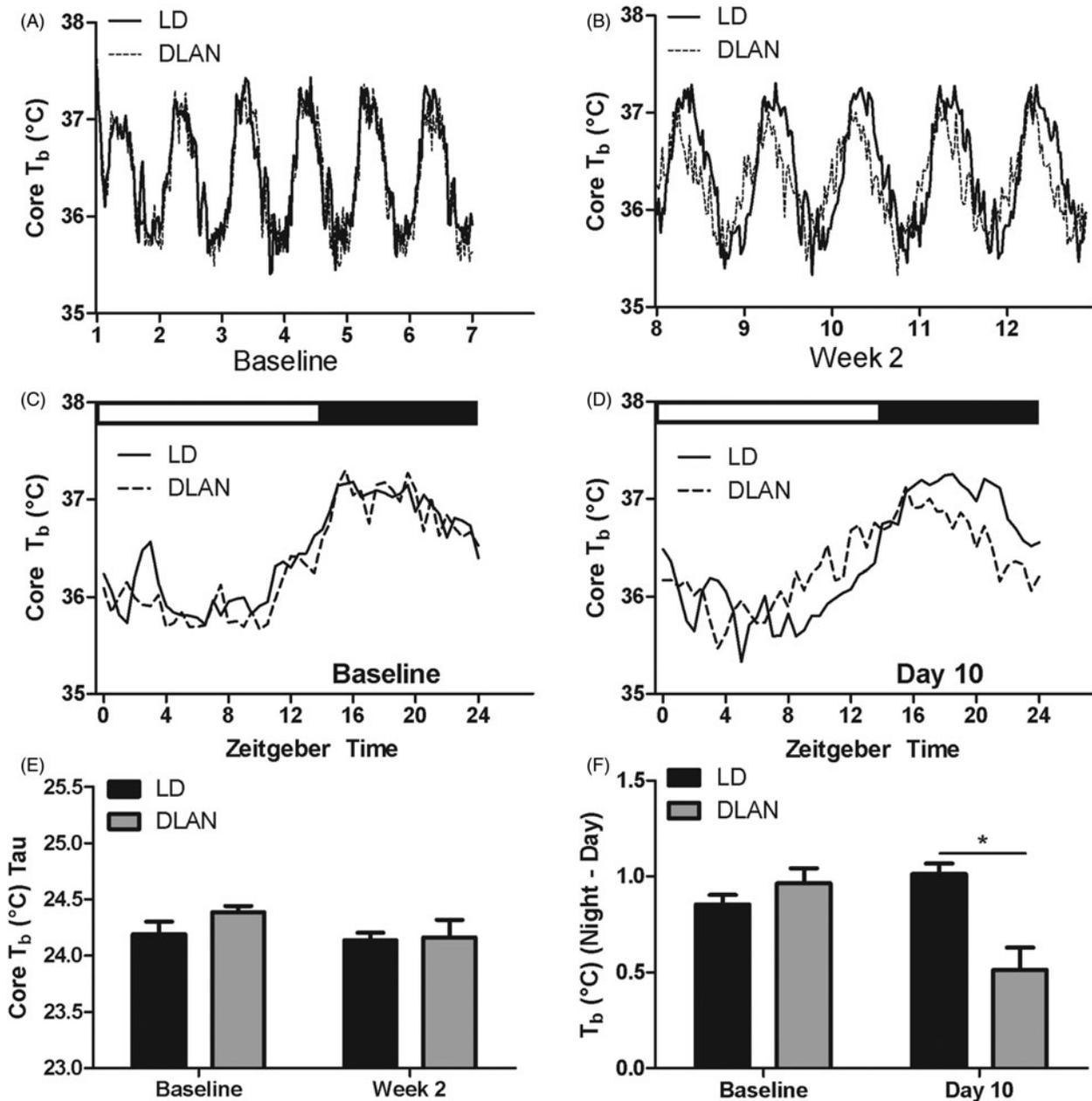


FIGURE 3. Short-term DLAN exposure alters core body temperature rhythms. (A) Core body temperature during the baseline week and (B) during days 8–12 of DLAN exposure. (C) Single day temperature rhythm at baseline and at (D) day 10 in DLAN conditions. (E) Period (tau) of body temperature rhythm at baseline and during the 2nd week of exposure to DLAN and (F) Body temperature difference between the dark and light phases at baseline and day 10. (Error bars represent SEM; $N=8-9$ per group; $*p<0.05$).

difference in T_b was not altered between baseline and day 10 in LD animals ($t(7)=2.2$, $p>0.05$), but was significantly decreased between sampling times in DLAN animals ($t(7)=2.5$, $p<0.05$). T_b period (tau) was unchanged in either the LD ($t(7)=0.532$, $p>0.05$) or DLAN ($t(7)=1.36$, $p>0.05$) group over the course of 2 weeks. To assess latency to peak T_b after lights off (15:00), maximum T_b was determined across the course of 24 h at baseline and day 10. At baseline, light condition groups did not differ in the latency to max T_b after lights off ($F_{1,14}=0.014$, $p>0.05$), with both groups reaching this max value ~ 4.3 h after lights off (Figure 3C). However, at day 10, in the middle of the 2nd

week of exposure, dim light animals reached their max $T_b \sim 3$ h earlier compared to dark night animals ($F_{1,14}=7.88$, $p<0.05$) (Figure 3D) indicating a significant shift in the rhythm of core body temperature. This phase shift may reflect an advance in the total rhythm of T_b or preferentially influence the decline phase of T_b .

DLAN and dark night exposed animals displayed similar activity rhythms at baseline (Figure 4A, C) ($F_{1,14}=0.828$, $p>0.05$) and at week 2 ($F_{1,14}=1.57$, $p>0.05$) analyzed via repeated measures ANOVA at baseline and at day 10 (Figure 4B, D). Period (tau) at baseline was equivalent between groups ($F_{1,14}=0.24$, $p>0.05$) and after 2 weeks of exposure to DLAN

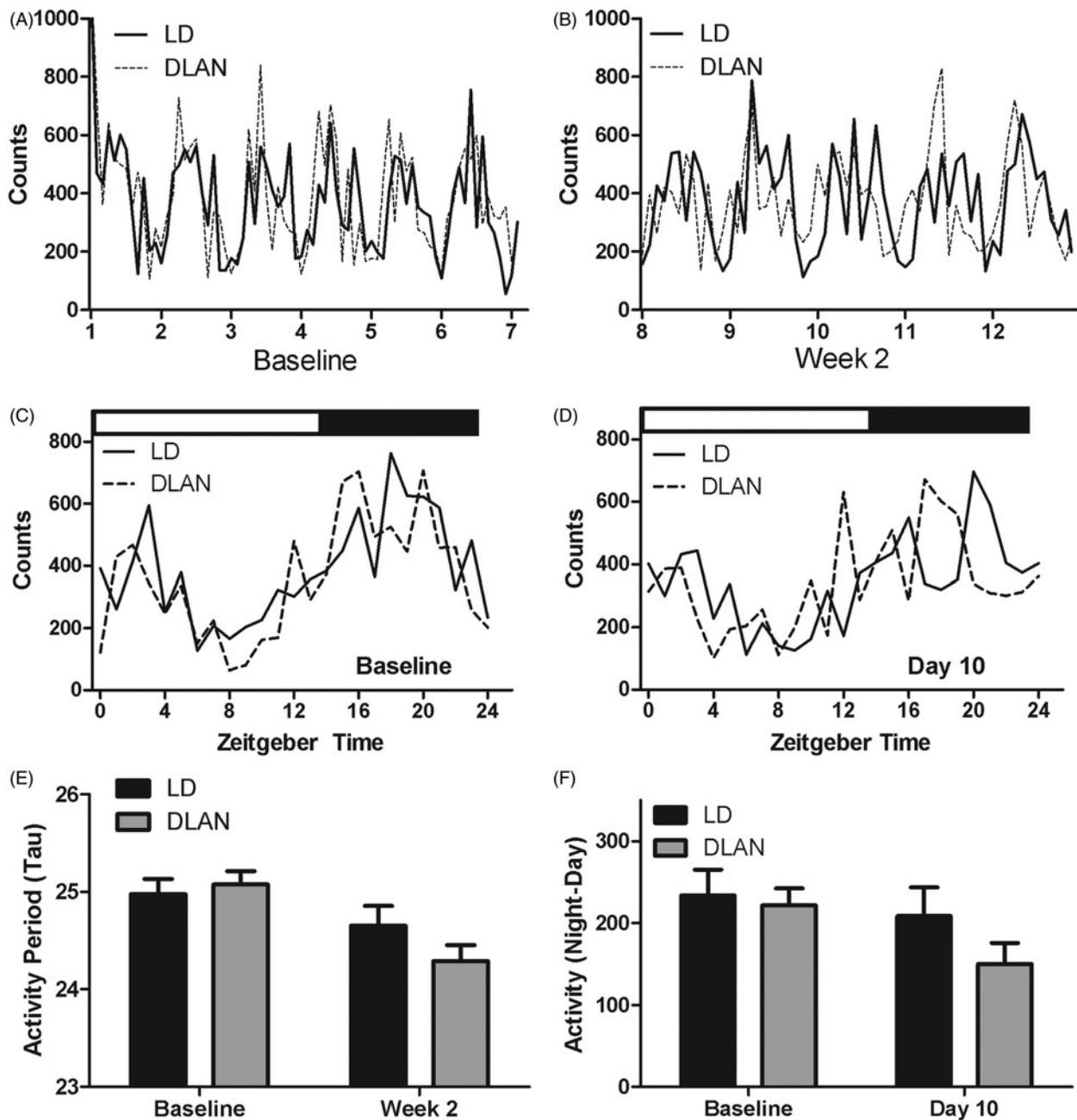


FIGURE 4. Gross locomotor activity rhythms are not altered by 2-week exposure to DLAN. (A) Minimitter activity output during the baseline week and (B) during days 8–12 of DLAN exposure. (C) Single day activity at baseline and at (D) day 10 in DLAN conditions. (E) Period (τ) of activity rhythms at baseline and during the 2nd week of exposure to DLAN and (F) activity difference between the dark and light phases at baseline and day 10. (Error bars represent SEM; $N=8-9$ per group).

($F_{1,14} = 1.97$, $p > 0.05$) (Figure 4E), indicating that DLAN did not cause arrhythmic activity over the 2-week exposure. In contrast to altered dark/light differences in T_b after 2 weeks of exposure to DLAN, the difference between dark and light phase activity levels did not differ at baseline ($F_{1,13} = 0.12$, $p > 0.05$) or after 2 weeks in DLAN ($F_{1,13} = 1.85$, $p > 0.05$) (Figure 4F). Additionally, the light/dark phase difference in activity was unchanged between baseline and week 2 in LD animals ($t(6) = 0.646$, $p > 0.05$) or DLAN animals ($t(7) = 2.26$, $p > 0.05$). Latency to peak activity after

active phase onset was similar between groups at baseline ($F_{1,14} = 0.166$, $p > 0.05$) and at day 10 ($F_{1,14} = 0.418$, $p > 0.05$), when T_b rhythms were shifted (Figure 3B, D). These data indicate that rhythms in T_b , but not activity, were significantly altered by DLAN. Activity period (τ) did decrease by an appreciable amount within the DLAN ($t(7) = 3.25$, $p < 0.05$) but not the LD group ($t(7) = 1.31$, $p > 0.05$) over the course of 2 weeks. Differences between light condition groups at week 2, however, were statistically non-significant. Despite changes in the rhythm of T_b and not activity,

the coupling of their peak values (Unc; described in methods) was unchanged at baseline ($F_{1,14} = 0.237$, $p > 0.05$) or by DLAN at day 10 ($F_{1,14} = 0.219$, $p > 0.05$).

DISCUSSION

Our data suggest that even short-term exposure (<2 weeks) to dim night-time light can influence several metabolic parameters. Within 2 weeks of housing in DLAN conditions, mice gained significantly more mass (Figure 1A, B) and altered metabolic output (Figure 2) and body temperature rhythms (Figure 3). These changes occurred despite similar food intake (Figure 1C), gross activity levels (Figure 1D), and circadian rhythms in activity (Figure 4).

The decrease in VO_2 that we observed across the dark \rightarrow light transition was reflected in decreased energy expenditure (heat) (Figure 2B, F) and an increased reliance on carbohydrates over fat for energy metabolism (Figure 2D). Increased RER may reflect increased propensity for fat storage, as less of this fuel was being utilized during the metabolic sessions in favor of carbohydrates. The decreased energy expenditure and altered fuel utilization likely contributed to the observed increase in mass gain (Figure 1A, B). Indeed, lower VO_2 consumption and energy expenditure, in conjunction with higher RER values are associated with increased adiposity in rodents and humans (e.g. Chitwood et al., 1996; Fan et al., 2005; Nestoridi et al., 2012; Ravussin et al., 1988; Wade et al., 1990).

Body mass significantly increases following chronic DLAN exposure (Fonken et al., 2010, 2013a), which is attributed to a shift in the timing of food intake to the inactive (light) phase and suppression of peripheral clock gene expression. As peripheral oscillators are entrained by the timing of food intake (Menaker et al., 2013; Mistlberger, 2011; Mistlberger & Antle, 2011; Stephan, 2002), altered ingestive timing likely contributes to peripheral clock gene expression abnormalities and mass gain (Lamia et al., 2008; Marcheva et al., 2010; Paschos et al., 2012). Peripheral clocks are (in contrast with the “master” clock located in the suprachiasmatic nuclei) also entrained by circadian rhythms in body temperature (Brown et al., 2002; Buhr et al., 2010; Kornmann et al., 2007). This allows the central oscillator to “set” the temperature rhythm without being influenced by its own output. We suggest that in addition to the altered timing of food intake (not assessed in this study), the shift (~ 3 h; Figure 3B, D) in T_b observed in the present study may further contribute to (or reflect) an “internal desynchrony” between central and peripheral oscillators. Indeed, such a phenomenon has been implicated in the development of metabolic abnormalities due to circadian disruption (Barclay et al., 2012; Damiola et al., 2000; Ramsey & Bass, 2009; Salgado-Delgado et al., 2010). Previously, we reported attenuation of hepatic and

white adipose tissue specific *Reverb- α* under DLAN conditions (Fonken et al., 2013a). This nuclear receptor acts as a repressor of *Bmal1* transcription and has recently been demonstrated to play a critical role in the regulation of body temperature (Gerhart-Hines et al., 2013), reaching peak expression levels in anti-phase with the T_b rhythm (Lazar, 2014). Altered T_b rhythms observed in the present study may therefore reflect altered expression of specific nuclear receptors that normally contribute to body temperature control. Body temperature rhythms “reset” peripheral clocks through a (as of yet) poorly defined mechanism likely involving the rhythmic expression of heat shock factor 1 (*Hsf1*) (Buhr et al., 2010; Reinke et al., 2008), which is also modulated (in the liver) by feeding time (Asher & Schibler, 2011; Katsuki et al., 2004).

Interestingly, the shift in T_b observed in the present study occurred without a significant change in the rhythm of gross locomotor activity (Figure 4), suggesting that these normally synchronized processes may have become uncoupled by DLAN exposure over the course of 2 weeks. However, this did not seem to be the case, as all mice showed similar phase relationships between T_b and activity rhythms at baseline and at day 10 in DLAN. This lack of difference may be explained by a shift in the value over the course of the 2-week period, as the time between T_b and activity peak was ~ 2.75 h at baseline, but shifted down to ~ 1.4 h in both groups at day 10. This may alternatively indicate that the week of recovery following telemeter implantation may not have been extensive enough to allow for full resynchronization to the light cycle prior to the start of the experiment. Nevertheless, it is important to note that the shift in T_b was directional, that is, the peak T_b moved ~ 3 h closer to “lights off” in DLAN conditions. This suggests that DLAN promotes a specific advance (as opposed to a delay) in the temperature rhythm under a 14:10 light/dim light cycle. The physiological significance of this shift requires further research.

Significant dampening of activity and T_b rhythms has been observed in obese Zucker rats with normal entrainment (Murakami et al., 1995). Obese women display lower mean temperatures, dampened rhythms, and lower quality daily rhythms than non-obese women (Cobalan-Tutau et al., 2011). Consistent with these previous findings, DLAN reduced the active-inactive phase difference in T_b (Figure 3F), reflecting a reduction in the contrast between day and night T_b . Lack of differences in this value in activity rhythms suggests T_b can be influenced independent of activity under DLAN conditions.

CONCLUSIONS

Our data highlight the short-term metabolic consequences of DLAN exposure. Consistent with previous findings, 2-week DLAN exposure elicited significant

mass gain (Fonken et al., 2010, 2013a, b), altered metabolic fuel utilization, and reduced energy expenditure. In addition to these metabolic phenotypes, an altered rhythm in core body temperature was observed independent of activity rhythms. This may reflect or contribute to “internal desynchrony” between central and peripheral circadian oscillators to contribute to metabolic dysfunction. Alternatively, the data presented in the present study may represent a circadian-independent response specifically to the direct actions of light. This is unlikely as previous studies on dim light exposure in mice have extensively characterized metabolic abnormalities with concurrent central and peripheral clock gene alterations (Fonken et al., 2013a). Further studies are required to examine “cause and effect” relationships between DLAN and body temperature rhythm abnormalities in the development of metabolic disease.

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DECLARATION OF INTEREST

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