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ORIGINAL ARTICLE

Light at Night Alters Daily Patterns of Cortisol and Clock Proteins in Female Siberian Hamsters

T. A. Bedrosian*, A. Galan*, C. A. Vaughn*, Z. M. Weil* and R. J. Nelson*

**Department of Neuroscience, Ohio State University Wexner Medical Center, Columbus, OH, USA.*

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Humans and other organisms have adapted to a 24-h solar cycle in response to life on Earth. The rotation of the planet on its axis and its revolution around the sun cause predictable daily and seasonal patterns in day length. To successfully anticipate and adapt to these patterns in the environment, a variety of biological processes oscillate with a daily rhythm of approximately 24 h in length. These rhythms arise from hierarchally-coupled cellular clocks generated by positive and negative transcription factors of core circadian clock gene expression. From these endogenous cellular clocks, overt rhythms in activity and patterns in hormone secretion and other homeostatic processes emerge. These circadian rhythms in physiology and behaviour can be organised by a variety of cues, although they are most potently entrained by light. In recent history, there has been a major change from naturally-occurring light cycles set by the sun, to artificial and sometimes erratic light cycles determined by the use of electric lighting. Virtually every individual living in an industrialised country experiences light at night (LAN) but, despite its prevalence, the biological effects of such unnatural lighting have not been fully considered. Using female Siberian hamsters (*Phodopus sungorus*), we investigated the effects of chronic nightly exposure to dim light on daily rhythms in locomotor activity, serum cortisol concentrations and brain expression of circadian clock proteins (i.e. PER1, PER2, BMAL1). Although locomotor activity remained entrained to the light cycle, the diurnal fluctuation of cortisol concentrations was blunted and the expression patterns of clock proteins in the suprachiasmatic nucleus and hippocampus were altered. These results demonstrate that chronic exposure to dim LAN can dramatically affect fundamental cellular function and emergent physiology.

Key words: *Phodopus sungorus*, PER1, PER2, BMAL1, light pollution

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Correspondence to:
T. A. Bedrosian, Department of Neuroscience, Ohio State University Wexner Medical Center, 636 Biomedical Research Tower, 460 West 12th Avenue, Columbus, OH 43210, USA (e-mail: bedrosian.2@osu.edu).

Life on Earth has adapted to a consistent 24-h solar cycle. Circadian rhythms in physiology and behaviour remain synchronised to the environment using light as the most potent entraining cue. During the past century, however, the invention and widespread adoption of electric light has led to 'round-the-clock' societies. Instead of aligning with the environment, individuals follow artificial and often erratic light cycles created by social and work schedules. Exposure to artificial light at night (LAN), termed 'light pollution', has become pervasive over the past 100 years. Virtually every individual living in the USA and Europe experiences this aberrant light exposure and approximately 20% of the population performs shift work (1,2). LAN may disrupt physiological timekeeping, leading to dysregulation of internal processes and misalignment between behaviour and the environment. Recent evidence suggests that individuals exposed to excessive LAN, such as night shift workers, have an increased risk for depressive disorders (3–6), breast cancer (7–9) and metabolic ailments (10). Given the growing list of health risks associated with excessive exposure to LAN, it is important to understand its underlying effects on physiology.

The circadian system may be influenced by LAN at several different levels. For one, nightly pineal melatonin secretion is suppressed by exposure to LAN (11,12), which may cause temporal misalignment between internal processes and the external environment. On another level, LAN may influence the diurnal rhythm of cortisol secretion from the adrenal gland. The suprachiasmatic nucleus (SCN) regulates hypothalamic-pituitary-adrenal axis function by sending direct neural input to the paraventricular nucleus of the hypothalamus. Finally, the expression of circadian clock genes and proteins in the SCN is directly modulated by light information. For

example, brief pulses of LAN can rapidly induce *Per1* gene expression (13), although the effects of chronic exposure remain unspecified. Disruption of the diurnal expression of clock genes and proteins may cause desynchronisation of central and peripheral clocks, contributing to serious health effects (14).

We investigated the effects of chronic exposure to dim (5 lux) LAN in female Siberian hamsters. This light intensity is approximately five times brighter than maximal moonlight, which is comparable to the levels of light pollution surrounding urban centres, and is sufficient to suppress pineal melatonin secretion in hamsters (12,15,16). Our experiments focus specifically on female hamsters because: (i) women are more likely to work evening or rotating shifts, thus encountering unnatural light exposure, and women have been implicated in many adverse health effects associated with LAN (8,17) and (ii) the effects of sleep disruption can be separated from the effects of LAN because these are nocturnal rodents that normally sleep during the light. With this in mind, we examined diurnal patterns in: (i) homecage locomotor activity; (ii) plasma cortisol concentrations; and (iii) clock protein expression in the brain, with the hypothesis that chronic exposure to LAN would cause disruption at each of these levels. We specifically investigated clock proteins in the SCN (i.e. the brain's master circadian clock) and the CA1 subregion of the hippocampus because previous studies reported CA1 hippocampal abnormalities in response to chronic LAN exposure (3,4).

Materials and methods

Animals

Adult female Siberian hamsters (*Phodopus sungorus*) were obtained from our breeding colony at The Ohio State University. Hamsters were individually housed in polypropylene cages (30 × 15 × 14 cm) at a constant ambient temperature of 22 ± 2 °C and a relative humidity of 50 ± 5%. Food (Teklad 8640; Harlan, Indianapolis, IN, USA) and filtered tap water were available *ad libitum*. Before starting the experiments, all hamsters (>8 weeks of age) were ovariectomised under isoflurane anaesthesia to prevent the effects of fluctuating oestrogens on clock protein expression, and then allowed to recover for 1 week. This species exhibits no clear changes in the profile of vaginal cell types, nor in vaginal discharge characteristics, and so determining the oestrous stage by these methods is unreliable (18). Following the recovery period, hamsters were maintained under either control or experimental light cycles as described below. The control condition was a 16 : 8 h light/dark cycle (150 lux/0 lux) and the experimental condition was a 16 : 8 h light/dim light cycle (150 lux/5 lux). Both the bright and dim lights were typical 'cool white' fluorescent bulbs. Under both conditions, the bright lights were off at 15.00 h (ZT12). All experimental procedures were approved by The Ohio State University Institutional Animal Care and Use Committee and conducted in accordance with the National Institute of Health (NIH) guidelines on laboratory animal use and care.

Homecage locomotor activity

Homecage locomotor activity was recorded over several days using an infrared beam break system (Columbus Instruments, Columbus, OH, USA). Data were analysed and actigraphs were constructed using CLOCKLAB software (Actimetrics, Wilmette, IL, USA).

Cortisol concentrations

Terminal blood samples were collected through heparinised capillary tubes from the retro-orbital sinus for radioimmunoassay of cortisol concentrations. Samples were collected from separate groups of hamsters at six different time points every 4 h to examine the diurnal pattern. Upon collection, blood samples were immediately centrifuged for 30 min at 3300 **g** and 4 °C, then plasma aliquots were stored at −80 °C until assayed. Total plasma cortisol concentrations were determined in duplicate using an ^{125}I antibody kit (MP Biomedicals, Solon, OH, USA). The high and low limits of detectability of the assay were 0.1 and 100 ng/ml, respectively. The intra-assay coefficient of variation was <10%. All procedures were performed in accordance with the respective manufacturer's instructions.

PER1, PER2 and BMAL1 expression

Brains were collected from separate groups of hamsters at six different time points every 4 h to examine the diurnal pattern of circadian clock protein expression. Briefly, hamsters were deeply anaesthetised with an overdose of sodium pentobarbital and transcardially perfused with ice-cold 0.1 M phophate-buffered saline (PBS) (pH 7.4), followed by 4% paraformaldehyde in 0.1 M PBS (pH 7.4). Following perfusion, brains were collected, post-fixed overnight at 4 °C, transferred to 30% sucrose solution in PBS at 4 °C until sunk, and then frozen in cold isopentane and stored at −80 °C. Brains were serially sliced into 30-μm sections using a cryostat and sections were thaw-mounted onto gelatin-coated glass slides and stored at −80 °C.

Sets of tissue collected at intervals of 120 μm were used for immunohistochemical detection of PER1, PER2 and BMAL1 throughout the SCN and hippocampus. Briefly, sections were incubated for 10 min in warm citrate buffer (pH 6.0) for antigen retrieval, then rinsed with 0.1 M PBS, and incubated for 30 min in 0.3% H_2O_2 in methanol. Sections were rinsed again in PBS, and then blocked for 1 h in 1% normal goat serum + 1% bovine serum albumin in 0.1 M PBS + 0.1% Triton. Sections were then incubated overnight at room temperature with the primary antibody (PER1, dilution 1 : 8000; PER2, dilution 1 : 10 000; BMAL1, dilution 1 : 500; provided by David Weaver, University of Massachusetts, Worcester, MA, USA). The specificity of these antibodies has been demonstrated in Syrian and Djungarian hamsters (19,20). Next, sections were rinsed, incubated for 1 h with anti-guinea pig immunoglobulin G (dilution 1 : 500; Southern Biotech, Birmingham, AL, USA) in 0.1 M PBS + 0.1% Triton. The signal was amplified with avidin-biotin complex (Vectastain Elite ABC Kit; Vector Laboratories, Burlingame, CA, USA) and developed using 3,3'-diaminobenzidine. Control sections were treated the same, except for omitting the primary antibody. Slides were dehydrated through a series of graded ethanol washes and cleared with xylene, then coverslipped using Permount (Fisher Scientific, Pittsburgh, PA, USA).

Images of sections containing mid-level SCN (Bregma −0.46 to −0.58) or rostral hippocampal cornu ammonis 1 (CA1) (Bregma −1.70) were obtained at × 10 magnification using an E800 bright-field microscope (Nikon, Tokyo, Japan). Numbers of immunoreactive cells were counted in IMAGEJ (NIH, Bethesda, MD, USA) by an observer who had no knowledge of the assignment to experimental groups, and then averaged across sections and sides of the brain to produce one value for each animal that was used for the statistical analysis. All cells were counted in SCN sections and a representative sampling of cells within a 300 × 100 pixel box was counted in the CA1.

Statistical analysis

Cortisol and clock protein data were analysed by two-way ANOVA with nighttime light condition (dark versus dim) and time of day as the independent variables. Main effects were followed up with Fisher's post-hoc comparisons.

Activity data were analysed by one-way ANOVA with light condition as the independent variable. Statistics were performed using STATVIEW, version 5.0.1 (SAS Institute, Cary, NC, USA). $P \leq 0.05$ was considered statistically significant.

Results

Locomotor activity

Locomotor activity log is presented for representative hamsters exposed to either dark (Fig. 1A) or dim LAN (Fig. 1B). Activity was mostly contained in the dark or dim light phase under both conditions. The overall power of the rhythm was modestly reduced in dim LAN, as indicated by a fast Fourier transform ($F_{1,13} = 4.609$, $P = 0.05$), although activity onset and acrophase were equivalent ($P > 0.05$) (Fig. 1C). Total 24-h activity counts were not significantly reduced in dim LAN (not shown; dark: 21958.5 ± 6725.8; dim LAN: 9662.6 ± 4692.8; $P > 0.05$). Duration of activity was not influenced by LAN (not shown; dark: 9.0 ± 0.91; dim LAN: 7.75 ± 0.38; $P > 0.05$).

Cortisol

The diurnal pattern of cortisol concentrations differed by night-time light condition ($F_{1,46} = 4.309$, $P < 0.05$); there was a distinct peak in cortisol at ZT15, with greater concentrations in the hamsters experiencing dark nights compared to hamsters exposed to dim LAN (post-hoc, $P < 0.05$; Fig. 1D). There were no time of day or interaction effects ($P > 0.05$).

Clock proteins

In the SCN, we detected an interaction between light and time for PER1 expression ($F_{5,55} = 2.767$, $P < 0.05$), with greater peak expression in dark nights compared to dim LAN at ZT15 (post-hoc, $P < 0.01$; Fig. 2). There were no main effects of time of day or light condition in SCN PER1 expression ($P > 0.05$). There was a main effect for time in PER2 expression ($F_{5,52}$=2.373, $P = 0.05$), again with greater peak expression in dark at ZT15 (post-hoc, $P < 0.05$; Fig. 3). There was no main effect of light, nor any interaction effects ($P > 0.05$). BMAL1 expression was constitutive, with no effect of light or time (Fig 4). In the CA1 region of the hippocampus, there were no effects of light or time, and no interaction effect in PER1 expression ($P > 0.05$; Fig. 5A,B). There was an interaction effect in PER2 expression ($F_{5,39} = 2.968$, $P < 0.05$), revealing greater expression in dark nights at ZT11 (post-hoc, $P < 0.01$; Fig. 5C,D), although no main effect of light or time ($P > 0.05$). There was no effect of light or time in BMAL1 expression in CA1 (Fig. 5E,F).

Discussion

The circadian system is adapted to a rhythm of bright days and dark nights. Only in very recent history has the adoption of electric lights allowed humans to escape the natural day/night rhythm. Humans are chronically exposed to artificial LAN and negative health consequences are only now becoming apparent. We explored the hypothesis that chronic exposure to dim LAN alters the circadian system at the level of locomotor activity patterns, the diurnal cortisol rhythm, and diurnal expression of core circadian clock

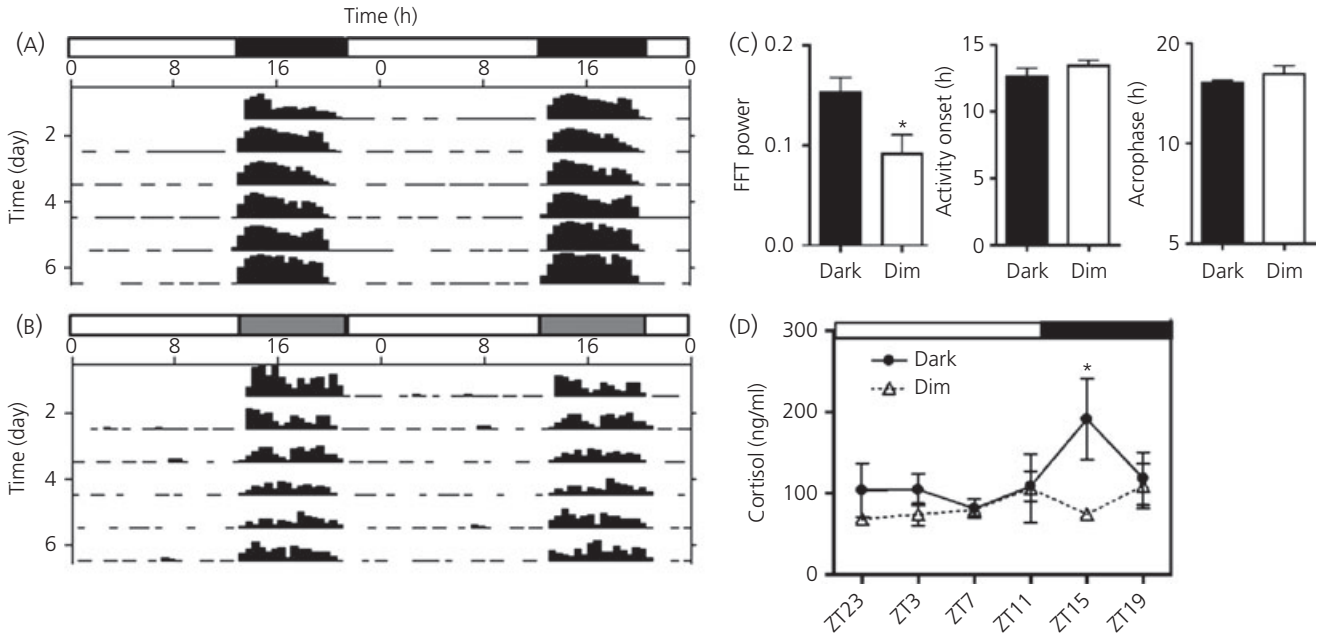

Fig. 1. Homecage locomotor activity and cortisol concentrations. Actigraphs showing that activity remains consolidated to the night in dark nights (A) and in dim light at night (LAN) (B). The strength of the rhythm is reduced in LAN, although activity onset and acrophase are equivalent to hamsters exposed to dark nights (C). The rhythm in diurnal plasma cortisol concentrations is abolished after exposure to LAN (D) (n = 3–6 per group). Graphs show mean ± SEM. *$P < 0.05$ at ZT15. FFT, fast Fourier transform.

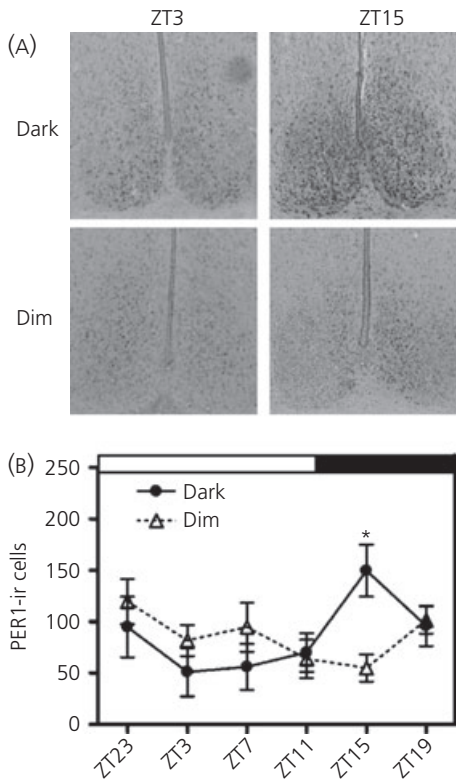

Fig. 2. PER1 expression in the suprachiasmatic nucleus. Representative images taken at × 10 magnification show trough and peak expression at ZT3 and ZT15 (A). Peak expression at ZT15 was abolished after exposure to light at night (B) (n = 3–8 per group). Graph depicts mean ± SEM. *P < 0.05 at ZT15. PER1-ir, PER1 immunoreactive.

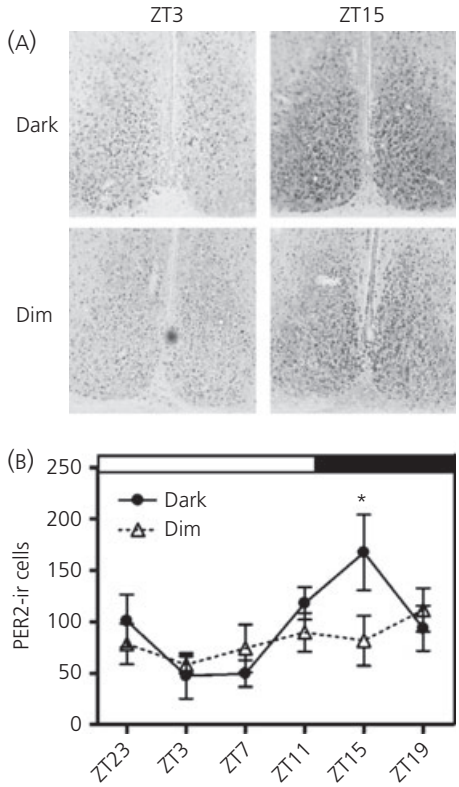

Fig. 3. PER2 expression in the suprachiasmatic nucleus. Representative images taken at × 10 magnification show trough and peak expression at ZT3 and ZT15 (A). Peak expression at ZT15 was abolished after exposure to light at night (B) (n = 3–7 per group). Graph depicts mean ± SEM. *P < 0.05 at ZT15. PER2-ir, PER2 immunoreactive.

proteins in female Siberian hamsters. Our results demonstrate that, although dim LAN does not overtly influence the entrainment of activity patterns, it does influence the strength of the activity rhythm, flatten the diurnal pattern of cortisol concentrations, and alter the expression of PER1, PER2 and BMAL1 in the SCN and hippocampus. Taken together, these findings suggest that modern night-time lighting may significantly affect physiology.

In the present study, we used fluorescent lights producing 150 lux during the day and 5 lux for night-time exposure. The spectral composition of fluorescent lighting is known to produce many peaks, although these are mainly restricted to shorter wavelengths, compared to tungsten filaments that produce a smooth spectral distribution peaking at red wavelengths (21). Although human and rodent retinas have a different spectral sensitivity, circadian and nonvisual effects of light are primarily mediated by a specific subpopulation of intrinsically photosensitive retinal ganglion cells (ipRGCs) that exhibit peak sensitivity at wavelengths of 446–488 nm in both species (21). Thus, even though rodent and human retinas have different spectral sensitivity of rods and cones, the ipRGCs that mediate circadian and nonvisual effects of light are sensitive to light in the same wavelength range in both humans and rodents. The fluorescent light used in the present study is likely effective for activating these cells in Siberian hamsters, just as it would be in humans.

By the same token that dim LAN is unnatural, complete darkness is also rare in nature. A light intensity comparable to moonlight or starlight can have effects on the circadian system. In this scenario, low level light appears to be advantageous. In Syrian and Siberian hamsters, a dim LAN of < 1 lux and as low as < 0.005 lux facilitates re-entrainment to different day lengths and increases the upper range of entrainment (22–24). There may be an optimal light intensity that confers advantages to organisms, whereas exceeding that intensity has deleterious effects. In support of this notion, the maximum intensity of moonlight is approximately 1 lux (15). Light intensities greater than this (and as little as 1.08 lux) suppress pineal melatonin content in Syrian hamsters (12). Furthermore, a number of recent studies document the effects of exposure to light at night. For example, songbirds living near streetlights have altered mating calls and lay eggs earlier than those living deep in the forest (25); bats that are in close proximity to streetlights change their commuting patterns, with no evidence of habituation over time (26); and beach mice living near populated coastlines display altered foraging behaviour (27).

Our data demonstrate that Siberian hamsters exposed to dim LAN remain entrained to the light cycle, although they exhibit slight decrements in the overall strength of the rhythm. Also, our data indicate that the daily rhythm in cortisol concentrations is abolished after chronic exposure to LAN. Typically, cortisol

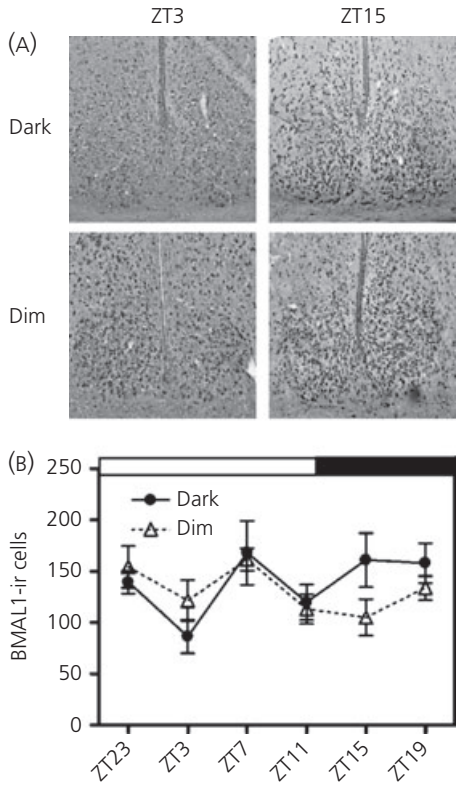

Fig. 4. BMAL1 expression in the suprachiasmatic nucleus. Representative images taken at × 10 magnification show expression levels at ZT3 and ZT15 (A). Expression was constitutive and not influenced by exposure to light at night (B) (n = 3–8 per group). Graph depicts mean ± SEM. BMAL1-ir, BMAL1 immunoreactive.

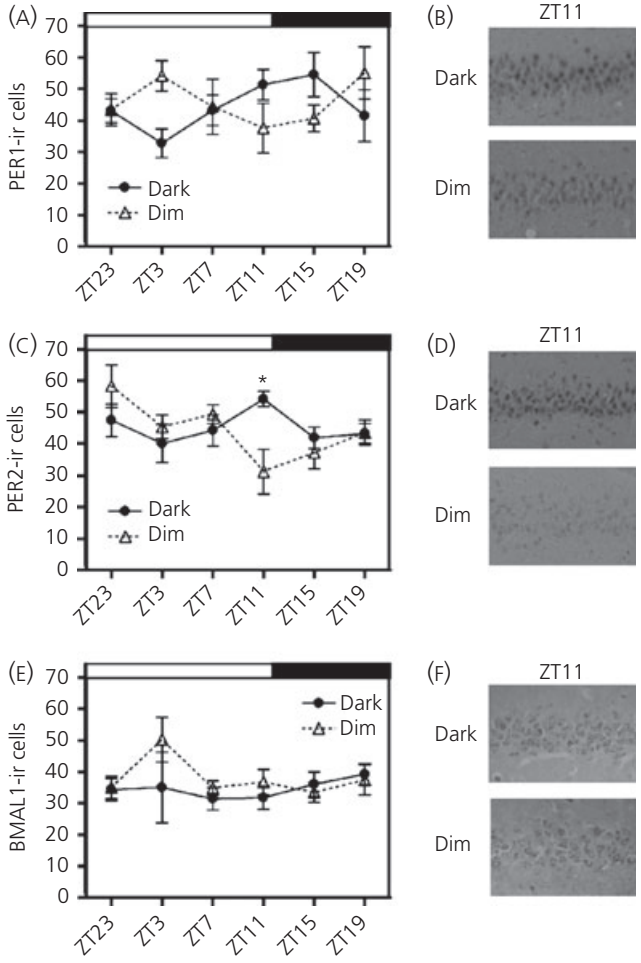

Fig. 5. PER1, PER2 and BMAL1 expression in CA1 hippocampus. Light at night did not change expression of PER1 (A, B), altered expression of PER2 (C, D) and did not influence BMAL1 expression levels (E, F) (n = 3–9 per group). Images taken at × 10 magnification. Graphs depict mean ± SEM. *P < 0.05 at timepoint indicated. PER1-ir, PER1 immunoreactive; PER2-ir, PER2 immunoreactive; BMAL1-ir, BMAL1 immunoreactive.

concentrations peak near the beginning of the active phase in both diurnal and nocturnal species (28). The cortisol rhythm secreted from the adrenal glands is under control of the circadian system. Light information received by the SCN is projected to the paraventricular nucleus of the hypothalamus, which in turn releases corticotrophin-releasing hormone, signalling the anterior pituitary to release adrenocorticotrophic hormone (ACTH) (29). The adrenal cortex is stimulated by ACTH to release cortisol (29). The lack of distinct light and dark signals to the SCN could disturb the diurnal rhythm in cortisol release, although chronic exposure to LAN may be necessary to see this effect. A 3-h light pulse of 600 lux administered to human volunteers during the night did not influence cortisol concentrations (30). However, an 8-week exposure to constant light decreased diurnal corticosterone levels and ablated the peak in female rats (31). To our knowledge, the present study is the first to show that low level night-time illumination, as might be commonly experienced in modern society, may be sufficient to alter the diurnal cortisol rhythm. Furthermore, it is possible that many humans are exposed to even greater light intensities at night as a result of multiple light sources indoors. More data on typical indoor light intensities are needed.

Our results also show that PER1 and PER2 expression in the SCN is altered with exposure to LAN, although BMAL1 expression remains unchanged. BMAL1 protein tends to be constitutively expressed in the mouse SCN at high levels, and its expression is unchanged by a light pulse occurring during the night (32). This supports our observations and may explain the lack of any influence of LAN on BMAL1 expression. PER1 and PER2, however, exhibited diurnal rhythms in hamsters exposed to a standard light/dark cycle, although the peak was reduced with dim LAN. Peak levels occurred in early night, which is consistent with other findings in this species (19). At the level of gene expression, the peak precedes the protein expression, occurring during the subjective day (33). Light pulses administered during the night are known to induce *Per1* gene expression, with a more limited induction of *Per2* (13,34). At the level of protein expression, a light pulse during the early night does not induce PER2 even 6 h later, and further PER2 levels are low and arrhythmic in rats exposed to constant light (35). The level of illumination used in the present study may have been sufficient to weaken or shift PER1 and PER2 expression. It will be important to determine the amount of light required to produce this change.

In previous studies, we have found that chronic exposure to dim LAN profoundly influenced the hippocampus. After 4 weeks,

dendritic structure on CA1 neurones was altered and *bdnf* gene expression was reduced (3,4). Accordingly, we specifically investigated the expression of PER1, PER2 and BMAL1 within the CA1 region of the hippocampus. The overall rhythm in PER2 expression differed in LAN-exposed hamsters, although the pattern of PER1 and BMAL1 expression was unchanged. Specifically, in hamsters exposed to dark nights, PER2 exhibited a small peak at the beginning of the night, which was reduced by LAN. Putatively, disrupted signals from the SCN could lead to altered clock protein expression in the other brain regions, including the hippocampus. PER2 protein is highly expressed in hippocampal pyramidal layers and *Per2* mutant mice have impaired long-term potentiation and fear-conditioning behaviour (36). The SCN sends indirect projections to the hippocampus via the thalamus (37) that could drive changes in clock proteins, or altered hormonal signals such as melatonin or cortisol could also putatively contribute to the changes in clock protein expression in this region.

The present study is the first to use low level night-time illumination (i.e. similar to the conditions experienced by many individuals in modern society) to examine the effects on diurnal rhythms. Chronic exposure to dim (5 lux) LAN is a seemingly innocuous manipulation that produces profound effects on the pattern of cortisol and clock protein expression. Subsequent to the adoption of electric light over the past approximately 130 years, individuals are frequently exposed to dim LAN. Televisions, computers, e-readers and streetlight leak from outside are potential sources of this unnatural light exposure. The present study was performed using female Siberian hamsters, and epidemiological studies have identified several risks associated with excessive LAN for women in particular, including the risk of breast cancer (7–9). Given that many breast cancers are oestrogen-dependent, it is important to understand the relationship between female steroid hormones and LAN. One limitation of the present study is that we ovariectomised the hamsters because staging of the oestrous phase was not possible. In the future, it will be important to investigate the effects of ovarian steroids in this model. Taken together, the circadian system is not adapted to unnatural LAN exposure; thus, it is important that we consider the potential influence of our technology and lifestyle choices on physiology and health.

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