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Dim light at night exacerbates stroke outcome

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Abstract

Circadian rhythms are endogenous biological cycles that synchronize physiology and behaviour to promote optimal function. These ~24-hr internal rhythms are set to precisely 24 hr daily by exposure to the sun. However, the prevalence of night-time lighting has the potential to dysregulate these biological functions. Hospital patients may be particularly vulnerable to the consequences of light at night because of their compromised physiological state. A mouse model of stroke (middle cerebral artery occlusion; MCAO) was used to test the hypothesis that exposure to dim light at night impairs responses to a major insult. Stroke lesion size was substantially larger among animals housed in dLAN after reperfusion than animals maintained in dark nights. Mice housed in dLAN for three days after the stroke displayed increased post-stroke anxiety-like behaviour. Overall, dLAN amplified pro-inflammatory pathways in the CNS, which may have exacerbated neuronal damage. Our results suggest that exposure to LAN is detrimental to stroke recovery.

Keywords

circadian rhythms; cytokines; light pollution; MCAO; neuroinflammation; stroke

1 | INTRODUCTION

The advent of electric lighting has revolutionized virtually every aspect of human life and has allowed marked advances in industrial productivity, quality of life and clinical medicine. However, this development has not come without costs; there is mounting evidence that

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AUTHOR CONTRIBUTIONS

Z.M.W., L.K.F., H.O.M.F., J.B., W.H.W., J.A.L. and N.Z. performed the experiment. Z.M.W., W.H.W. and L.K.F. analysed the data. Z.M.W., L.K.F. and H.O.M.F. wrote the manuscript. R.J.N. and A.C.D. designed the experiment and edited the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

PEER REVIEW

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chronic exposure to artificial light at night, though convenient, can have unforeseen but serious, negative effects on health outcomes ranging from cardiometabolic disease to cancer (Haus & Smolensky, 2013; Lunn et al., 2017; Rybnikova, Haim, & Portnov, 2016). Moreover, there is also the possibility that acute exposure to light at night and the resulting circadian disruption could exacerbate disease outcomes in vulnerable populations (Penev, Kolker, Zee, & Turek, 1998; Simons, Van den Boogaard, & Jager, 2019).

Critically ill patients obviously benefit from the ability of clinicians to monitor and treat their conditions at all times of the day. Modern intensive care is characterized by a number of processes that can lead to circadian disruption including noise from monitors and staff, frequent waking for procedures and vital checks and light at night (Korompeli et al., 2017; Pulak & Jensen, 2016). Moreover, critically ill individuals may be particularly vulnerable to the unintended negative consequences of artificial lighting that occurs in the intensive care setting (Chan et al., 2012; Freedman, Gazendam, Levan, Pack, & Schwab, 2001; Nelson & DeVries, 2017).

There are several potential links between circadian disruption and poor disease outcomes among the critically ill. First, acute illnesses, such as sepsis and stroke, can dampen circadian rhythmicity, impair sleep and suppress daily patterns of melatonin secretion (Freedman et al., 2001; Li et al., 2013; Meng, Liu, Borjigin, & Wang, 2008); furthermore, disruption of circadian cues by the ICU environment may further exacerbate negative outcomes. Additionally, there are endogenous daily rhythms in the vulnerability to tissue damage and in tissue remodelling after injury that are critical determinants of long-term outcomes from acute injury (Alibhai et al., 2014; Weil et al., 2009).

Patients who undergo an ischaemic stroke may be one such vulnerable population as they have sustained brain damage and often require recovery in the ICU (Langhorne & Baylan, 2017). Ischaemic brain injury occurs when the blood and nutrient supplies to the brain fail to meet tissue requirements. Although focal ischaemic injuries typically induced by vessel occlusion produces a central core of degenerating tissue, there is often a surrounding region, referred to as the penumbra, that is compromised, but potentially viable (Astrup, Siesjo, & Symon, 1981). Indeed, the survival of penumbral tissue is a determinant of long-term functional outcomes and supporting the survival of those cells is a major goal of ischaemia research (Rogers, Campbell, Stretton, & Mackay, 1997). Recently, we reported that artificial dim light at night exacerbates the cell death and inflammatory responses to cardiac arrest and cardiopulmonary resuscitation, a global ischaemic injury (Fonken et al., 2019). Here, we hypothesized that exposure to dim white light, at night during the period after experimental focal ischaemic stroke would increase infarct size, exacerbate inflammatory responses and impair functional outcomes compared to animals housed in dark night conditions.

2 | METHODS

2.1 | Animals

Male Swiss-Webster mice (8–10 weeks of age) were obtained from Charles River Laboratories (Wilmington, MA). Prior to surgical procedures, all animals were individually housed in a 14:10 light-dark (LD) cycle with ad libitum access to standard rodent chow

(Harlan Teklad 8640; Madison, WI, USA) and filtered tap water. Animals were allowed to acclimate to the laboratory environment for at least one week following arrival before any additional manipulations. All experimental procedures were approved by the Ohio State University and West Virginia University Institutional Animal Care and Use Committees and were conducted in accordance with NIH guidelines.

2.2 | Surgical procedures

Ischaemic stroke was induced with a middle cerebral artery occlusion (MCAO) paradigm as previously described (Craft et al., 2005; Craft, Zhang, Glasper, Hurn, & Devries, 2006). All surgical procedures occurred during the light phase (zeitgeber time (ZT) 9–13). Briefly, mice were deeply anesthetized (until unresponsive to a toe pinch) with isoflurane vapours and a unilateral right MCAO was achieved by insertion of a 6–0 nylon monofilament into the internal carotid artery to a point 6 mm beyond the internal carotid pterygopalatine artery bifurcation. Body temperature was maintained at $37 \pm 0.5^{\circ}\text{C}$ through the use of a homeothermic blanket system. Once the occluder was secured, the wound was sutured and the animal was allowed to awaken from anaesthesia. After 60 min of occlusion, the animal was re-anesthetized and reperfusion was initiated by removal of the occluder. Animals were allowed to recover in cages partially atop warming pads set to 37°C before return to their home cages. Surgical sites were carefully monitored to assure that there was no infection or wound dehiscence.

2.3 | Lighting manipulations

Following the reperfusion, mice were transferred to either dark night conditions (LD 14-hr light (125 lux, 33.2 mW/cm^2); 10-hr dark (0 lux, 0 mW/cm^2) or dim light at night conditions (dLAN) [14-hr light (125 lux, 33.2 mW/cm^2); 10-hr dim light (5 lux/ 1.8 mW/cm^2)], (Experiment 1, $N = 11\text{--}13/\text{group}$), dLAN or LD conditions (Experiment 2, $N = 12/\text{group}$). Dim light at night was broad-spectrum white light produced with strips of LED lighting (Super Bright LEDs, St. Louis, MO, USA). Mice were maintained in the lighting conditions through the end of the experiment.

2.4 | Behavioural testing

Open-field testing occurred 72 hr after MCAO. The testing chambers had $40 \text{ cm} \times 40 \text{ cm}$ clear acrylic walls lined with corncob bedding, inside a ventilated cabinet (Med Associates, St. Albans, VT USA). A frame at the base of the chamber comprising 32 photobeams in a 16×16 arrangement, in addition to a row of beams above, detected the location of horizontal movements and rearing, respectively (Open Field Photobeam Activity System, San Diego Instruments Inc., San Diego, CA USA). Movement was recorded for 20 min. Percentage of beam breaks in the centre of the open field, number of rears and total locomotor behaviours was assessed as a measure of general locomotor activity and anxiety-like behaviour.

3 | TISSUE COLLECTION

3.1 | Experiment 1

Survival plots were generated from mice that survived up to seven days post-reperfusion. At seven days post-reperfusion, mice were deeply anesthetized with isoflurane vapours and

decapitated and brains collected. As there was low overall survival to seven days, subsequent behavioural experiments and tissue collections occurred 72 hr post-reperfusion.

3.2 | Experiment 2

To quantify infarct volume in a separate cohort of animals, brain tissue was collected 72 hr post-MCAO surgery, immediately after behavioural testing.

3.3 | Determination of stroke infarct size

Brains were sectioned into five 2-mm-thick coronal sections and incubated for 15 min with 2,3,5-triphenyltetrazolium (TTC) at 37°C (Bederson et al., 1986; Craft et al., 2005), which stains live mitochondria. Slices were fixed in 10% buffered formalin for 3–5 days and then photographed; infarct area throughout the forebrain was analysed using Inquiry software (Loats Associates, Inc. Westminster, MD USA). Infarct size was determined as a percentage of the contralateral hemisphere after correcting for oedema, using the following formula: $[1 - (\text{total ipsilateral hemisphere} - \text{infarct}) / \text{total contralateral hemisphere}] \times 100$. Infarct size was analysed by an individual unaware of experimental group assignments.

3.4 | Experiment 3

A separate cohort of animals was used to assess acute effects of light at night on inflammatory responses. As animals were euthanized after 24 hr (deeply anesthetized with isoflurane and decapitated), no survival curves were generated. After 24 hr in LD or dLAN housing ($n = 12/\text{group}$), bilateral samples of the cortex were collected and total RNA was extracted by using a homogenizer (Powergen 1000, Fisher Scientific, Indianapolis, IN, USA) and a RNeasy Mini Kit (Qiagen, Valencia, CA, USA) according to the manufacturer's protocol. Extracted RNA was resuspended in 40 μl of RNase-free water, and RNA concentration was determined by a spectrophotometer (NanoDrop 1000, NanoDrop Technologies, Wilmington, DE, USA). The following inventoried primers and probes (Applied Biosystems, Forester City, CA, USA) were used: IL-6, IL-1 β and TNF- α . A TaqMan 18S rRNA primer and probe set, labelled with VIC dye (Applied Biosystems, Forester City, CA, USA), was used as a control gene for relative quantification.

3.5 | Statistical analysis

Survival analysis was conducted using a Wilcoxon analysis of Kaplan-Meier survival curves. Behavioural outcomes, infarct size and PCR results were assessed via a one-way ANOVA (lighting conditions). All significant overall results ($p < .05$) were followed up with least significant difference post hoc analyses. Data related to this article are available upon reasonable request to the corresponding author and are also available in Figshare.

4 | RESULTS

Housing animals in dim light at night after stroke did not reduce overall survival over the seven days following reperfusion ($\chi^2 = 3.781$, $p = .0518$, Figure 1a). Subsequent experiments focused on 72 hr post-reperfusion time points. Three days after reperfusion, mice that were housed in dLAN after ischaemia exhibited no difference in total locomotor activity ($F_{1,27} = 0.019$, $p = .890$, $\eta^2 = 0.001$, data not shown). However, there was a

significant reduction in central exploratory activity among mice that were exposed to dLAN compared to those in dark nights ($F_{1,27} = 5.38$, $p = .028$, $\eta^2 = 0.166$ Figure 1b). Moreover, stroke lesion size was substantially larger among animals that were housed in dLAN after reperfusion than animals maintained in dark nights ($F_{1,23} = 5.264$, $p = .031$, $\eta^2 = 0.186$, Figure 1c).

Analysis of gene expression 24 hr post-reperfusion was performed in a cohort of animals. In the ipsilateral cortex, gene expression for TNF α ($F_{2,18} = 6.044$, $p = .01$, $\eta^2 = 0.402$, Figure 2), IL6 ($F_{2,18} = 4.227$, $p = .031$, $\eta^2 = 0.320$) and IL-1 β ($F_{2,18} = 5.723$, $p = .012$, $\eta^2 = 0.389$) was significantly altered by lighting conditions. For all three genes, expression was higher among mice housed in dLAN as compared to mice housed in dark nights. There were no effects of lighting conditions on cytokine gene expression in the cortex contralateral to the ischaemic lesion ($p > .05$).

5 | DISCUSSION

The adoption of artificial lighting has dramatically shaped human life. However, it is becoming increasingly clear that there are substantial reasons to be concerned about the potential effects of artificial light at night on human health, particularly for individuals with critical illnesses (Korompeli et al., 2017; Nelson & DeVries, 2017). Stroke is an example of a health condition that typically requires several days of hospitalization under conditions that often include exposure to night-time light, which in turn may disrupt circadian rhythms and sleep (Durrington et al., 2017; Pulak & Jensen, 2016). Whether circadian disruption as a result of the hospital environment is unintentionally exacerbating disease outcomes remains an unanswered, but important question (Nelson & DeVries, 2017). Indeed, many of the negative consequences of the ICU for health outcomes have historically been attributed to disrupted sleep. Our studies of nocturnal mice (that typically sleep during the light phase) demonstrate that although sleep is a highly salient output of circadian clocks, disruption of the central circadian clockwork is sufficient to produce poor outcomes (Alibhai et al., 2014; Fonken et al., 2019; Penev et al., 1998). Further, we have previously shown that sleep is not disrupted by dim light at night in house mice (Borniger, Weil, Zhang, & Nelson, 2013) indicating that sleep disruption is unlikely to drive the current phenomenon. Finally, similar light at night manipulations can impact circadian rhythms without significantly altering stress axis physiology (Walker *et al.*, 2020).

Here, we demonstrate that one component of the disruptive effects of the hospital environment, exposure to dim light at night, *after* experimental cerebral ischaemia significantly exacerbates ischaemic outcomes as indicated by reduced survival, larger infarct sizes, more post-stroke anxiety-like behaviour and increased expression of pro-inflammatory cytokines in the injured hemisphere. These data are consistent with previous findings from our group that circadian disruption with dim light at night exacerbates hippocampal cell death and inflammatory responses following global ischaemic injuries (Fonken et al., 2019).

Focal cerebral ischaemic injuries are dynamic combinations of differentially damaged tissue. At the centre or core of ischaemic lesions are a population of cells that are irreversibly damaged. However, surrounding this core lesion is a heterogenous population of cells that

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were impaired by reductions in blood flow, but potentially salvageable. Current stroke interventions are designed to restore blood flow to infarcted tissue in order to minimize the proportion of this penumbral region that will become part of the core infarct over the subsequent days and weeks (Chamorro, Dirnagl, Urra, & Planas, 2016). The temporal delay between onset of ischaemic injury and the final loss of damaged tissue (Heiss, 2012) means that events in the early post-ischaemic period have the potential to influence the final infarct size and functional impairments. Although this is typically considered a therapeutic advantage because it allows a wide window in which to administer treatment, our data suggest that the physical characteristics of the recovery environment can be detrimental to recovery. In the current study, light manipulations began several hours after ischaemic reperfusion, indicating that this manipulation altered cell death in the penumbra rather than the core.

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Therefore, the critical question is how circadian disruption, induced by dim light at night, alters the survival of the ischaemic penumbra in the hours to days following reperfusion. The pathophysiological events that occur in the penumbra are complex and involve overlapping contributions from inflammation, uncontrolled depolarization, oxidative damage, impairments in energy metabolism and decoupling of energy needs from vascular responses (Moskowitz, Lo, & Iadecola, 2010). In general, however, events that further exacerbate the metabolic deficits induced by prolonged ischaemia such as energetically costly spreading depolarizations decrease the likelihood that penumbral tissue survives.

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One potential link between acute circadian disruption and ischaemic cell death is neuroinflammation. Prolonged exposure to dim light at night can increase pro-inflammatory cytokine expression in the normal brain and potentiate both central and peripheral inflammatory responses to acute inflammatory stimuli such as lipopolysaccharide (Bedrosian, Weil, & Nelson, 2013; Fonken, Weil, & Nelson, 2013). Moreover, acute dim light exposure potentiates inflammatory responses to global cerebral ischaemia (Fonken et al., 2019). Microglia and other immune cells express circadian clock genes, which are important regulators of both normal physiology and the responses to inflammatory stimuli (Keller et al., 2009; Silver, Arjona, Hughes, Nitabach, & Fikrig, 2012). Indeed, there are strong daily rhythms in the inflammatory response of microglia both in vivo and in vitro (Fonken et al., 2015). Further, dim light at night disrupts molecular circadian rhythms and thus may interfere with the regulation of inflammatory responses following ischaemia.

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Ischaemic stroke induces acute inflammatory responses via multiple mechanisms. The alteration in blood flow and initiation of the clotting cascade can both induce expression of cell adhesion molecules that can lead to extravasation of leucocytes into the injured parenchyma (del Zoppo & Mabuchi, 2003). Moreover, disruptions in the parenchymal microenvironment by metabolic distress, damage-associated molecular patterns (DAMPs) and related events can activate tissue-resident microglia and astrocytes leading to acute activation of inflammatory events (Chen & Nunez, 2010). In the present study, dim white, but not red, light at night augmented the expression of the mRNAs for pro-inflammatory cytokines IL-1 β , IL-6 and TNF α . Early increases in gene expression of these cytokines can potentiate ischaemic cell death (Lambertsen, Biber, & Finsen, 2012). The design used in the current study cannot rule out that dim light-induced increase in pro-inflammatory cytokine

gene expression results from the greater ischaemic lesion rather than being the cause of it. Indeed, debris from degenerating cells also is a major driver of inflammatory events in the injured CNS (Shichita, Ito, & Yoshimura, 2014). However, data from our previous study indicated that pharmacological inactivation of pro-inflammatory cytokine signalling was sufficient to prevent the dim light-induced increase in cell death following global ischaemia (Fonken et al., 2019). Thus, it seems likely that increases in inflammatory signalling are necessary for dim light-induced increases in infarct size.

Other potential causal links between acute dim light at night and exacerbation of ischaemic outcome include disruptions of daily rhythms in vulnerable tissues. Circadian rhythmicity allows for coordination both within and between physiological systems. One consequence of these rhythms is that tissue can systematically vary in its vulnerability to injury. The same injury can produce different functional impairments and tissue loss depending on when it is administered (Weil et al., 2009) indicating that tissue is differentially susceptible to pathology even under normal conditions. Moreover, acute illnesses such as stroke or sepsis themselves significantly impair circadian rhythmicity in several physiological processes including the rhythmic production of melatonin, clock gene expression and sleep (Gaudet et al., 2018; Korpelainen, Sotaniemi, Huikuri, & Myllyla, 1997; Li et al., 2013; Meng et al., 2008). Thus, exogenous circadian disruption, such as light at night, is occurring on top of already dampened circadian rhythms, with potentially significant health consequences. The precise temporal regulation of processes that would seem likely to support tissue survival is thus lost. For instance, cardiomyopathic hamsters exposed to chronic phase shifts had significantly greater mortality than those housed in fixed cycles (Penev et al., 1998). Even a much shorter period (5 days of a disruptive light cycle (10L:10D) after experimental myocardial infarction) exacerbated early inflammatory responses and interrupted tissue remodelling in the injured heart even when measured weeks later (Alibhai et al., 2014). Furthermore, other rodent models of circadian disruption, such as chronic phase advance, also increase infarct volume and result in higher mortality in response to ischaemic stroke (Earnest, Neuendorff, Coffman, Selvamani, & Sohrabji, 2016). Taken together, these data suggest that injured or diseased tissue is more likely to function and survive when under conditions of intact circadian rhythms.

One strength of the current study is that it allows for the teasing apart of some of the key components of circadian disruption that are common to the ICU environment. One commonly studied endpoint is sleep which is significantly disrupted among ICU patients and can also be impaired among individuals experiencing a stroke (Boyko, Jennum, & Toft, 2017). Although sleep was not directly assessed here, we have previously reported that in this strain of mice, dim light at night does not significantly impair sleep parameters (Bomiger et al., 2013). This may occur, at least in part, because mice are nocturnal and typically sleep during the light phase. However, even in the absence of sleep disruption light at night aggravated ischaemic pathology.

Post-ischaemic dim light at night also exacerbated anxiety-like behaviour as indicated by avoidance of the centre of the open-field chamber. This decreased central tendency was apparent in animals with larger infarct sizes so it is difficult to determine whether this is mediated by larger tissue loss and a greater inflammatory response or is a consequence of

the dLAN itself. Depression and anxiety are common among individuals who have experienced a stroke, a phenomenon termed post-stroke depression (Robinson & Jorge, 2016). This acute depressive state can be attributed, at least in part to increases in inflammatory signalling after injury (Craft & DeVries, 2006). Moreover, we have previously reported that prolonged dLAN can increase anxiety- and depression-like behaviours via increases in TNF signalling as pharmacological blockade of TNF prevents the increase in depressive- and anxiety-like behaviour (Bedrosian, Vaughn, et al., 2013). The increase in pro-inflammatory cytokine gene expression, here, is thus likely to be the mechanism underlying greater anxiety-like behaviour among the animals housed in dLAN.

These data provide significant evidence that one primary component of the ICU environment, light at night, has the potential to significantly exacerbate the tissue loss and functional impairments associated with focal cerebral ischaemia. Circadian disruption is thus an understudied, but likely critical, feature of the critical care environment, and future studies should examine the role of circadian disruption in the regulation of acute inflammatory responses to injury.

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Abbreviations:

CNS	central nervous system
CT	circadian time
dLAN	dim light at night
ICU	intensive care unit
IL-1β	interleukin-1 beta
IL-6	Interleukin-6
LD	light-dark
LED	light-emitting diode
MCAO	middle cerebral artery occlusion
SCN	suprachiasmatic nucleus
TNFα	tumour necrosis factor alpha

ZT

zeitgeber time

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FIGURE 1.

Dim light at night (dLAN) did not significantly alter survival (a) but did exacerbate functional impairments and cell death. Animals housed in dLAN after stroke (b) spent less time in the centre of the open-field chamber and (c) had larger infarcts than did animals housed in dark nights (LD). *Significantly different from LD at $p < .05$. Data are expressed as mean ($\pm$ SEM). $N = 11-13$ /group

FIGURE 2.

Light at night increased pro-inflammatory gene expression. dLAN potentiated the gene expression of the pro-inflammatory cytokines tumour necrosis factor alpha (TNF α), interleukin-6 (IL-6) and IL-1. Data are presented for the hemisphere ipsilateral (ipsi) and contralateral (contra) to the ischaemic lesion. *Significantly different from LD at $p < .05$. Data are expressed as mean ($\pm$ SEM). $N = 12$ /group