Research report

Influence of light at night on murine anxiety- and depressive-like responses

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ABSTRACT

Individuals are increasingly exposed to light at night. Exposure to constant light (LL) disrupts circadian rhythms of locomotor activity, body temperature, hormones, and the sleep-wake cycle in animals. Other behavioural responses to LL have been reported, but are inconsistent. The present experiment sought to determine whether LL produces changes in affective responses and whether behavioural changes are mediated by alterations in glucocorticoid concentrations. Relative to conspecifics maintained in a light/dark cycle (LD, 16:8 light/dark), male Swiss-Webster mice exposed to LL for three weeks increased depressive-like behavioural responses as evaluated by the forced swim test and sucrose anhedonia. Furthermore, providing a light escape tube reversed the effects of LL in the forced swim test. LL mice displayed reduced anxiety as evaluated by the open field and elevated-plus maze. Glucocorticoid concentrations were reduced in the LL group suggesting that the affective behavioural responses to LL are not the result of elevated corticosterone. Additionally, mice housed in LD with a clear tube displayed increased paired testes mass as compared to LL mice. Taken together, these data provide evidence that exposure to unnatural lighting can induce significant changes in affect, increasing depressive-like and decreasing anxiety-like responses.

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1. Introduction

With the advent of electrical lighting at the turn of the 20th century, individuals of many species, including humans, became exposed to bright and unnatural light at night. Urban development has further exacerbated the issue of light at night as lighting from infrastructure strays into the atmosphere. This "light pollution" is now affecting 99% of the population in the US and Europe and 62% of the world population [26]. Electric lights have not only created light pollution, but have permitted shift work at night, generally perturbing the sleep-wake patterns of humans [33]. Individuals exposed to light at night are at increased risk for heart disease [17], cancer [10,35], sleep disturbances [12,20], circadian rhythm dysfunctions [3], disrupted rhythmicity of neuroendocrine function (such as corticotrophin releasing hormone, glucocorticoids, and prolactin) [7,30], mood disorders [13], and reproductive dysfunction [14,36].

Housing animals in constant light (LL) conditions is useful for studying the effects of light at night in animal models. The majority of studies indicate that maintaining animals in LL conditions is deleterious, but the mechanisms underlying these harmful effects remain unspecified [26]. Continuous exposure to light strongly suppresses circadian rhythms of locomotion, body temperature, and the sleep-wake cycle of rodents [18], as well as generally elevating corticosterone concentrations [1,38]. It is possible that exposure to light at night produces harmful effects on animals directly via disruption of biological clock function [28]. Another possibility, albeit not mutually exclusive, is that light exposure at night represents a chronic stressor [22] which can indirectly affect physiological and behavioural processes [21].

Seasonal lighting, abnormalities in circadian clock [2], and sleep disorders are associated with depression in some subpopulations [5]. Although depression is traditionally considered maladaptive in humans, depressive-like behavioural responses persist in other species and may be advantageous under certain conditions. For example, symptoms of human seasonal affective disorder (SAD), such as lethargy, anxiety, altered food intake, and loss of sexual behaviour may be adaptive and conserve energy during the reduced day lengths of winter for individuals of some rodent populations [32]. This study is designed to address whether another form of circadian disruption, light at night, also negatively impacts affective behaviour. Depressive behaviours in humans may have evolved under a similar seasonal context as that of rodents and remain

susceptible to changes in environmental lighting. The unnatural light cycles to which humans are now exposed, and the irregular sleep patterns evoked by light at night, may interfere with typical responses to the annual cycle of changing day lengths.

Reports on the interaction of LL with depressive- and anxiety-like responses have been inconsistent. Although previous studies have reported altered brain morphology due to LL [21] and other forms of circadian disruption such as sleep deprivation [43], previously reported behavioural effects of LL are inconsistent. For example, LL has been reported to both influence memory [22] and have no effect on memory [6]. Additionally, although circadian disruption has been reported to lessen anxiety [34], the effect of LL on anxiety has not been well established [6,22].

In the present experiment, we examined behavioural and glucocorticoid responses to LL exposure, focusing on the possible link between altered lighting and affective responses. Male Swiss-Webster mice were housed in either LL or a light/dark cycle. We attempted to ameliorate the stress-evoking effects of constant light by providing half the mice with an opaque tube to serve as a light escape. As a control for the environmental-enriching effects of the tube, half of the mice were provided with a clear tube. We hypothesized that LL would increase corticosterone concentrations and elevate depressive-like behavioural responses and that providing light escape would partially reverse these effects.

2. Experimental procedures

2.1. Animals

Twenty-four male Swiss-Webster mice (∼8 weeks of age) were obtained from Charles River Labs (Kingston, NY) for use in this study. The mice were individually housed in propylene cages (30 cm × 15 cm × 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 all mice were maintained under a 16:8 light/dark (lights on at 23:00 Eastern Standard Time [EST]) cycle for one week to allow them to entrain to local conditions and recover from the effects of shipping. Following the recovery period, mice were randomly assigned to either a control or experimental treatment group. Mice assigned to the control group (n = 12) were maintained under a 16:8 light/dark (LD) cycle (lights on at 23:00 EST), whereas the experimental group was maintained in constant light (LL; n = 12) for the remainder of the study. The mice were housed in separate rooms with fluorescent ceiling lights controlling the light condition to which the mice were exposed. Each cage was provided with a PVC tube (length = 13.0 cm; inner diameter = 5.2 cm; outer diameter = 6.0 cm) that was either opaque providing light escape (LE; n = 12), or clear (C; n = 12). All experimental procedures were approved by The Ohio State University Institutional Animal Care and Use Committee, and animals were maintained in accordance with the recommendations of the National Institutes of Health and the *Guide for the Care and Use of Laboratory Animals*.

2.2. Experimental design

After three weeks in lighting conditions, the mice underwent a battery of behavioural tests to measure anxiety- and depressive-like responses. All testing occurred during the light phase between 8:00 and 13:00 EST with the exception of the sucrose anhedonia test (see below). Testing occurred in the following order to minimize stress effects in the most sensitive tests [8]: open field, elevated-plus maze, sucrose anhedonia, Porsolt forced swim test. Following testing, the mice were killed and their adrenals, spleens, testes, and fat pads were collected and weighed. Blood samples were collected immediately prior to the start of the experiment, after two weeks of experimental light condition, and at death.

2.3. Behavioural tests

To assess locomotor behaviour and anxiety-like responses, mice were placed in a 40 cm × 40 cm clear acrylic chamber lined with corncob bedding, inside a ventilated cabinet (Med Associates, St. Albans, VT). Mice were allowed to acclimate to the testing room for 30 min before testing began. The test chambers were rinsed with 70% ethanol and the bedding was changed between each test. The center of the open field was defined as the central 30 cm × 30 cm. A frame at the base of the chamber consisting of 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). Total movement was tracked for 30 min and analysed for: (1) the percentage of beam breaks in the center of the open field, (2) number of rears, and (3) total loco-
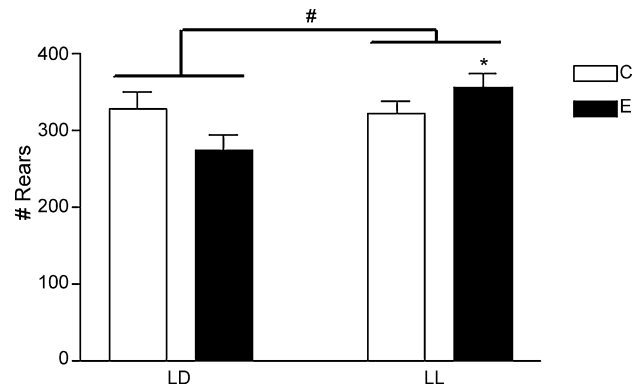

Fig. 1. Mean (±Standard Error of the Mean (SEM)) number of rears in the open field test for anxiety-like behaviours. Total duration of test was 30 min. #p < 0.05 between LL and LD groups; *p < 0.05 across light and tube type.

motor behaviour. Increases in central tendency and rearing are generally interpreted as low anxiety-like responses [9].

To further assess anxiety-like responses, mice were placed in a maze elevated 1 m above the floor made of dark-tinted acrylic and consisting of two open arms bisected by two arms enclosed by walls (the top of the entire maze was open) [16]. Prior to testing, mice were allowed to acclimate to the room for 30 min. Mice were placed in the central maze area facing a closed arm and recorded on video for 5 min. The maze was wiped with a mild soapy water solution between tests. An open arm entry was scored when the two forepaws and half of the body entered an open arm. A condition-blind observer using Observer software (Noldus Corp., Leesburg, VA, USA) scored tapes for: (1) latency to enter an open arm, (2) total time spent in the open arms, and (3) number of open arm entries.

Consumption of a 3% sucrose solution over 5 h during the active phase, 15:00–20:00 EST, was recorded in all mice to measure sucrose anhedonia [40]. Prior to the presentation of the sucrose solution, mice were administered tap water in modified water bottles for three consecutive nights, to control for novelty of the modified water bottles. The modified water bottles were weighed before and after the 5 h sample time to quantify the liquid volume consumed. After the three nights of tap water measurements, a 3% sucrose solution was provided for two nights. Sucrose consumption during both nights was normalized to the average pre-testing water consumption.

To assess depressive-like responses, mice were placed in room-temperature (22 ± 1 °C) water ∼17 cm deep, within an opaque, cylindrical tank (diameter = 24 cm, height = 53 cm). Swimming behaviour was recorded on video for 5 min and scored by a condition-blind observer with the Observer software (Noldus Corp.). Latency to float, total number of floating bouts, and total time spent floating served as dependent measures. High percent time floating is interpreted as an increased depressive-like response [31].

2.4. Radioimmunoassay

Blood samples (∼0.20 ml) were collected for radioimmunoassay (RIA) of corticosterone from the retro-orbital sinus of mice prior to entering the experimental treatment condition, after two weeks of experimental light condition, and at death. Blood samples were allowed to clot, the clot was removed, and the samples were centrifuged at 4 °C for 30 min at 6000 rpm. Serum aliquots were then aspirated and stored in sealable polypropylene microcentrifuge tubes at −80 °C until assayed. Total serum corticosterone concentrations for mice were determined in duplicate using an ICN Diagnostics ^{125}I double antibody kit (Costa Mesa, CA, USA). The high and low limits of detectability of the assay were 1200 and 3 ng/ml, respectively. All procedures were followed as described by the manufacturer guidelines.

2.5. Statistical analyses

Main effects of light condition (LD, LL) and tube condition (LE, C), and interactions thereof, on behavioural measures were assessed using one-way analysis of variance (ANOVA). *Post hoc* statistical analyses were performed using unpaired *t*-tests because pair-wise comparisons were limited. Mean differences were considered statistically significant when p ≤ 0.05.

3. Results

3.1. Open field

LL and LE affected rearing in the open field ($F_{1,20}$ = 5.488; p < 0.05; Fig. 1). Among LL mice, presence of an LE tube in the home cage sig-
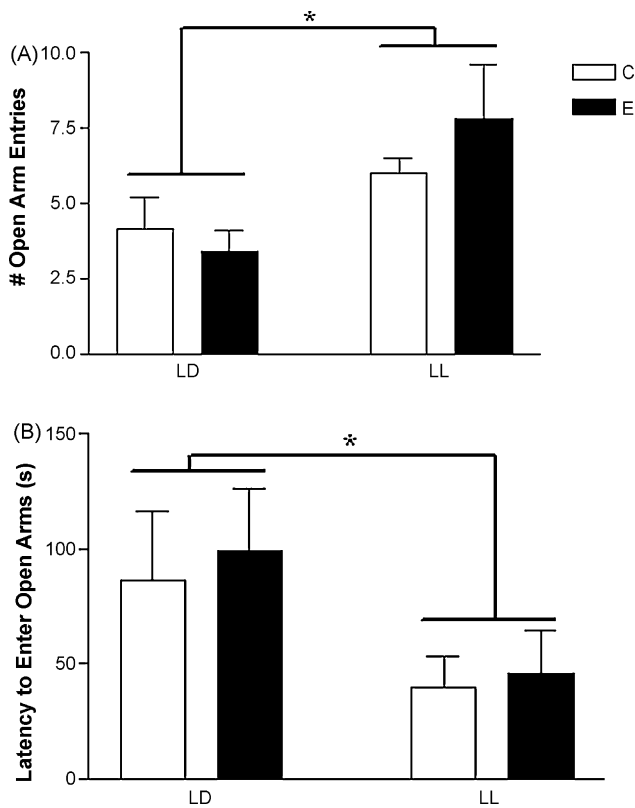
Fig. 2. Mean (±SEM) number of open arm entries (A), and latency (sec) to enter the open arm (B) in the elevated-plus maze test for anxiety-like behaviours. Total duration of test was 300 s. *$p < 0.05$ between LL and LD groups.

Fig. 3. Mean (±SEM) quantity of sucrose consumed on day 1 of a sucrose anhedonia test for depressive-like behaviour (g–g). Sucrose administration spanned 5 h each day. *$p < 0.05$ between LL and LD groups.

Fig. 4. Mean (±SEM) total float time (s) (A), and number of floating bouts (B) during Porsolt forced swim test for depressive-like responses. Total duration of test was 300 s. *$p < 0.05$ across light and tube type.

nificantly increased rearing behaviour ($t_{10} = -3.160$; $p < 0.01$; Fig. 1); in mice housed in a light–dark cycle (LD), in contrast, LE tubing significantly reduced rearing ($t_{10} = 2.204$; $p < 0.05$). Neither lighting conditions nor the type of tube affected locomotor activity or central tendency ($p > 0.05$ in each case).

3.2. Elevated-plus maze

Irrespective of LE, LL significantly affected latency to enter the open arms and number of open arm entries in the elevated-plus maze. Mice maintained in LL displayed shorter latencies to enter the open arms ($F_{1,19} = 4.531$; $p < 0.05$; Fig. 2A) and entered the open arms more frequently ($F_{1,19} = 8.452$; $p < 0.01$; Fig. 2B) as compared to the LD group. Neither lighting condition nor type of tube affected the duration of time spent in the open arms ($p > 0.05$).

3.3. Sucrose anhedonia

Sucrose consumption was significantly lower for the LL group as compared to the LD group on day one of sucrose anhedonia ($F_{1,20} = 4.225$; $p < 0.05$; Fig. 3A), although, these effects waned by day two ($p > 0.05$; data not shown).

3.4. Porsolt forced swim test

LL and LE affected the duration of time spent floating in the forced swim test ($F_{1,20} = 10.241$; $p < 0.01$; Fig. 4A). Mice housed in LL with a clear tube significantly increased float time relative to LD mice ($t_{10} = -3.595$; $p < 0.01$; Fig. 4A) and LL mice with LE tubing ($t_{10} = 3.485$; $p < 0.01$; Fig. 4A). Floating bouts were similarly affected by LL and home cage tubing ($F_{1,20} = 5.461$; $p < 0.05$; Fig. 4B). Clear
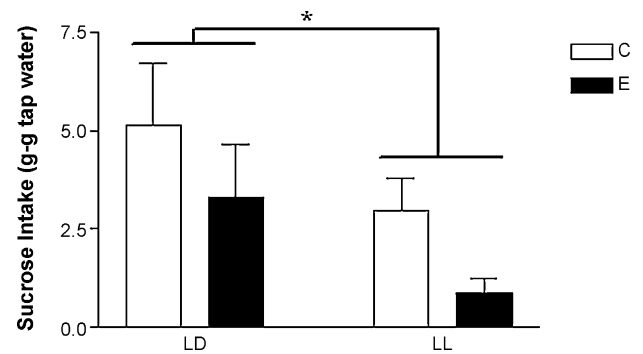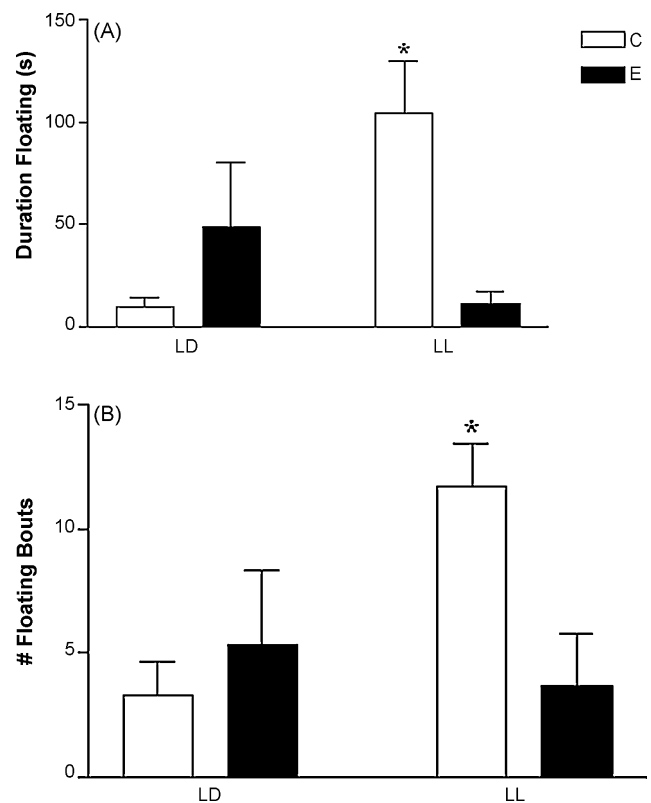
tubing significantly increased the number of floating bouts within the LL group ($t_{10} = 2.936$; $p < 0.05$; Fig. 4B) and as compared to LD mice with clear tubing ($t_{10} = -3.795$; $p < 0.01$).

3.5. Somatic measures

LL and LE interacted to affect paired testes weight ($F_{1,20} = 5.385$; $p < 0.05$; Fig. 5); mice maintained in LD and provided clear tubes had increased testes mass as compared to LL mice with a clear tube ($t_{10} = 2.842$; $p < 0.05$) and LD mice with opaque tubes ($t_{10} = 2.436$; $p < 0.05$). Neither lighting condition nor tube type had an effect on absolute and corrected (for body mass) fat pad, adrenal or spleen weights. Additionally, LL and LE had no effect on body mass ($p > 0.05$).
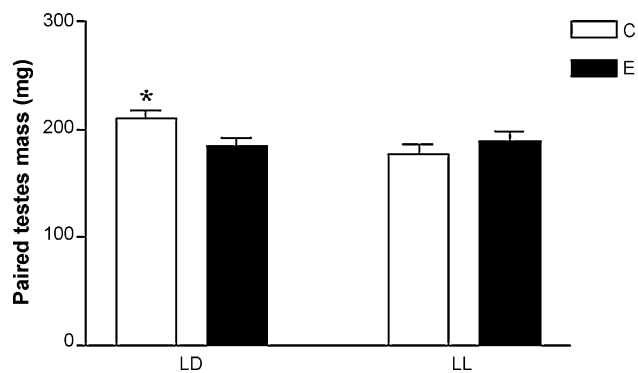
Fig. 5. Mean (±SEM) paired testes mass (mg). $*p < 0.05$ across light and tube type.

3.6. Corticosterone concentrations

There were no group differences in corticosterone concentrations upon entry into the experimental treatment conditions ($p > 0.05$, data not shown). After two weeks in light condition, LL mice had significantly reduced serum corticosterone concentrations as compared with LD mice ($F_{1,20} = 13.855$; $p > 0.01$). However, at death (six weeks) only LL mice housed with an LE tube had significantly depressed corticosterone concentrations ($F_{1,20} = 6.658$; $p > 0.05$).

4. Discussion

The goal of this study was to test the hypothesis that constant light would induce significant behavioural changes in Swiss-Webster mice. Specifically, we predicted that exposure to LL would increase stress-related parameters altering affective responses in behavioural tests and that providing an opportunity for LE would partially reverse these effects. Relative to conspecifics maintained in an LD cycle, male mice exposed to three weeks of LL increased depressive-like responses. Furthermore, the ability to escape LL exposure by entering an opaque tube reversed this effect in the forced swim test. LL mice reduced anxiety-like responses as evaluated by the open field and elevated-plus maze. Locomotor activity levels in an open field were unaffected by LL. Taken together, these results indicate that unnatural lighting can induce significant changes in affective behaviour; increasing depressive-like and decreasing anxiety-like responses. The role of stress steroid hormones in this process remains unclear, as glucocorticoid concentrations were lower in the LL group.

The effects of LE tubing on depressive-like behaviour varied between the forced swim test and sucrose anhedonia, whereas LL consistently increased depressive-like behavioural responses. Increased floating time in the forced swim test is considered "behavioural despair" because mice putatively stop searching for an escape mechanism [31]. Mice exposed to LL floated more frequently and for an extended duration in the forced swim test, exhibiting more behavioural despair than mice in LD conditions (Fig. 4). The presence of an LE tube, however, reversed float frequency and duration, which suggests, that the ability to escape light or self-regulate lighting quelled the depressive effects. This may reflect the effects of better sleep architecture, but sleep was not tested in the present study; again, nocturnal mice are generally exposed to bright light during the day in the laboratory when they sleep. In the sucrose anhedonia test, regardless of the option of LE, LL mice consumed less sucrose, suggesting diminished hedonic valence [40] (Fig. 3). The agreement between tests on the effects of LL supports our prediction that continuous lighting induces depressive-like behaviour. Discrepancies in the effect of tubing on depression between the two tasks could be the result of order effects. Stress alters depressive-

like behaviour [39]; therefore, stress produced by handling mice between tests may have affected the results. Alternatively, the opaque tubes may have prevented mice from viewing the tubes of sucrose water when they were placed in the cage influencing consumption; however, this is unlikely because there were no group differences in water consumption from the same modified bottles. The depressive-like phenotype of the LL mice is consistent with our predictions based on depressive disorders related to both stress [39] and circadian dysfunction [37].

Differences in anxiety-like behaviour were observed between LL and LD mice regardless of tubing type. Specifically, mice housed in LL had decreased anxiety-like behaviour as evaluated by the open field (Fig. 1) and elevated-plus maze (Fig. 2). Although there were no differences in central tendency or locomotion in the open field, mice maintained in LL reared more frequently which is indicative of decreased anxiety [9]. Constant light generally has a stimulant effect in the open field [1,6]. However, the open field was conducted during the light phase (inactive period) which may have contributed to the lack of an LL effect in the present study. Results from the elevated-plus maze parallel those obtained in the open field; mice in LL had a shorter latency to enter the open arms and entered the open arms more frequently than mice housed in an LD cycle; a decrease in open arm exploration is demonstrative of anxiety-like responses [16]. Previous research on LL and anxiety has been inconclusive. For example, LL reduced anxiety-like behaviour in rats as evaluated in the elevated-plus maze [22]. A study in Swiss EPM-M1 mice did not report differences in anxiety-related behaviours as evaluated in a plus-maze discriminative avoidance task; however, this task primarily evaluates learning and memory with a secondary focus on anxiety [6]. Additionally, the elevated-plus maze protocol employed in our study is the most widely used anxiety test by pharmaceutical companies testing anxiolytic drugs [11] with a high predictive validity [8].

The differential effect of LL on anxiety and depressive-like behaviours may seem counterintuitive given the co-morbidity of such disorders clinically [4]. However, modulation of different hormones and neurotransmitters including serotonin [15] and GABA, which are active in the suprachiasmatic nucleus (SCN), can produce opposite spectrum anxiety and depressive-like behaviours. For example, $GABA_{B(1)}^{-/-}$ mice, which lack functional $GABA_B$ receptor, have a behavioural interaction similar to LL mice, but in the opposite direction. That is, $GABA_{B(1)}^{-/-}$ mice express higher anxiety-like responses and increased resistance to stress-induced behavioural despair compared with mice with intact GABA receptors. Additionally, activation of the $GABA_B$ receptor with GABA receptor positive modulator GS37983 results in anxiolysis and treatment with a $GABA_B$ receptor antagonist CGP56433A results in antidepressant-like effects in animal models [24].

In contrast to our prediction, LL did not increase corticosterone concentrations; rather, corticosterone concentrations were lower in the LL group as compared with the LD group after two and six weeks in experimental light condition (Fig. 6). Because LL mice in our study had been exposed to a possibly stressful environmental situation (i.e., LL) for several weeks, they may have down-regulated their stress response; consequently, glucocorticoid concentrations were not elevated for the LL group when assayed by week two. In human studies, extreme stress results in lowered glucocorticoid concentrations, likely by dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis [19,42]. Another possible explanation for the lack of elevated circulating corticosterone is that the glucocorticoid rhythm is masked in the LL mice. Abolishing the circadian system by SCN lesions eliminates rodent corticosterone rhythms [25]. It is unlikely that the differences in corticosterone concentrations reflected differences in circadian phase because the blood draws occurred during the inactive period for the LD group, a point at which low concentrations of corticosterone would be expected. Two previous
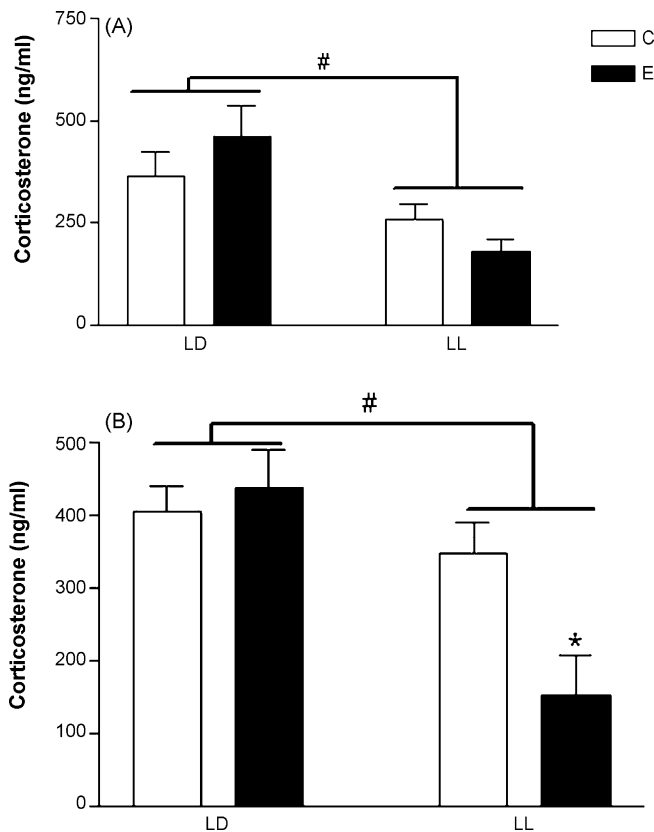
Fig. 6. Mean (±SEM) circulating corticosterone concentrations (ng/ml) at two weeks (A) and at death (B). #$p < 0.05$ between LL and LD groups; *$p < 0.05$ across light and tube type.

studies reported elevated circulating corticosterone concentrations in rodents housed in LL, however, both studies looked at circulating corticosterone in a different context [1,38]. Moreover, corticosterone concentrations were increased in mice exposed to LL for one week [38]. Because we did not measure corticosterone concentrations until week two, our results may reflect longer exposure to LL. Additionally, corticosterone values were obtained in LL rats after they received a subcutaneous injection and were evaluated in an open field [1] indicating that LL may mask corticosterone rhythms, but still induce a strong reaction to another stressor such as exposure to an open field. mPer2$^{-/-}$ mice lack functional glucocorticoid rhythms, despite exhibiting a robust corticosterone response to hypoglycemia, ACTH, and restraint stress [41]. The reduced glucocorticoid concentrations in the LL group suggest that the behavioural results of this study are not a byproduct of increased corticosterone concentrations. However, the overall effect of stress is unclear.

One unexpected result from our study was the difference in testes mass between groups (Fig. 5). LD mice housed with clear tubes had significantly larger testes mass across tube and light condition suggesting that deviation from the LD cycle by either exposure to constant light or by entrance into an LE tube may affect testes mass. The reproductive systems of inbred laboratory rats and mice are generally unresponsive to photoperiod [27]. However, LL affects reproductive function in male and female rats [23,29]. Our results confirm and extend these previous findings to mice.

In summary, our data provide evidence that exposure to continuous light can induce significant changes in affective responses in male Swiss-Webster mice. The present study has important implications because it indicates that nighttime light may lead to depressive-like disorders. These results are particularly salient for rodent vivaria that are designed with windows in the doors of animal rooms and continuous lighting in the halls. Further studies are necessary to quantify the minimum amount of nighttime light that results in a depressive-like phenotype and to elucidate the potential role of sleep disruption and stress in this process.

Acknowledgments

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