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Dim light at night provokes depression-like behaviors and reduces CA1 dendritic spine density in female hamsters

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Summary The prevalence of major depression has increased in recent decades; however, the underlying causes of this phenomenon remain unspecified. One environmental change that has coincided with elevated rates of depression is increased exposure to artificial light at night. Shift workers and others chronically exposed to light at night are at increased risk of mood disorders, suggesting that nighttime illumination may influence brain mechanisms mediating affect. We tested the hypothesis that exposure to dim light at night may impact affective responses and alter morphology of hippocampal neurons. Ovariectomized adult female Siberian hamsters (*Phodopus sungorus*) were housed for 8 weeks in either a light/dark cycle (LD) or a light/dim light cycle (DM), and then behavior was assayed. DM-hamsters displayed more depression-like responses in the forced swim and the sucrose anhedonia tests compared with LD-hamsters. Conversely, in the elevated plus maze DM-hamsters reduced anxiety-like behaviors. Brains from the same animals were processed using the Golgi-Cox method and hippocampal neurons within CA1, CA3, and the dentate gyrus were analyzed for morphological characteristics. In CA1, DM-hamsters significantly reduced dendritic spine density on both apical and basilar dendrites, an effect which was not mediated by baseline cortisol, as concentrations were equivalent between groups. These results demonstrate dim light at night is sufficient to reduce synaptic spine connections to CA1. Importantly, the present results suggest that night-time low level illumination, comparable to levels that are pervasive in North America and Europe, may contribute to the increasing prevalence of mood disorders.

1. Introduction

The prevalence of major depression and other mood disorders has dramatically increased in recent decades; however, the factors contributing to this phenomenon remain unspecified (Simon and VonKorff, 1992; Compton et al., 2006).

Abbreviations: AD, apical dendrite; BD, basilar dendrite; DG, dentate gyrus; DM, dim light at night condition; LD, standard light—dark condition.

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Better diagnoses or changing diagnostic criteria have traditionally been suggested as possible contributory factors; however, additional variables are likely involved. For instance, environmental influences play a role in the onset of depressive disorders and it is possible that recent environmental changes may partially account for the change in incidence.

One such environmental change which emerged during the 20th century is the growing prevalence of exposure to artificial light at night. The advent of electrical lighting permitted humans to stray from natural day—night cycles and this change has been widespread. In 2001, greater than 62% of the world's population, and more than 99% of those individuals living in the U.S. and Europe, experienced brighter than normal night skies (Navara and Nelson, 2007). Furthermore, about 20% of the population in any urban economy works night shifts and is chronically exposed to night-time illumination (Rajaratnam and Arendt, 2001). Because exposure to light at night suppresses secretion of the pineal hormone melatonin, which has anti-depressant effects on mood and hippocampal plasticity (Crupi et al., 2010), there may be a link between the rising rates of depression and nighttime light exposure.

The role of light at night in mood has been almost entirely unexplored due to a lack of animal models, and particularly in females, despite a two-fold increase in the incidence of depression among women compared to men (Kessler et al., 1993). Our laboratory recently demonstrated a depression-like phenotype in male mice exposed to constant bright light conditions (Fonken et al., 2009), but the effects of low level illumination at night, similar to what humans experience, have not yet been described. In particular, little is known of the extent to which light at night affects neural circuitry involved in mood.

The hippocampus is a critical structure in the pathophysiology of depressive disorders. Depressed patients show characteristic hippocampal atrophy (Sheline et al., 1999; Frodl et al., 2002), as well as dysregulation of many hippocampus-related systems, such as stress coping and memory (Halbreich et al., 1985; McEwen, 2003; Gallassi et al., 2006). Moreover, loss of hippocampal dendritic spines and synaptic inputs to spines are observed in animal models of depression (Hajszan et al., 2005, 2009, 2010). Interestingly, melatonin has actions directly in the hippocampus (Musshoff et al., 2002) and anti-depressant effects on mood (Crupi et al., 2010; de Bodinat et al., 2010). Furthermore, melatonin was recently shown to ameliorate the reduced spine density seen in a mouse model of depression (Crupi et al., 2010).

In order to begin investigating how light at night influences mood and hippocampal plasticity we exposed female hamsters, ovariectomized to prevent confounding estrogen effects on hippocampal morphology (Woolley and McEwen, 1992), to dim light at night, at a level sufficient to suppress melatonin secretion (Brainard et al., 1982). We hypothesized that chronic exposure to dim light at night would provoke depression-like responses in ovariectomized hamsters and alter dendritic morphology in the hippocampus.

2. Materials and methods

2.1. Animals

Seventeen 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 cm × 15 cm × 14 cm) at a constant ambient temperature of 22 ± 2 °C and relative humidity of 50 ± 5%. Food (Harlan Teklad 8640, Indianapolis, IN, USA) and filtered tap water were available ad libitum. Prior to starting the experiments, all hamsters (>8 weeks of age) were ovariectomized under isoflurane anesthesia and allowed to recover for ≥3 weeks. Following the recovery period, hamsters were maintained for 8 weeks in either control or experimental lighting conditions. Control animals ($N = 8$) remained in the standard colony room under a 16:8 light/dark cycle (LD; 150 lx/0 lx), whereas the experimental group ($N = 9$) was housed in a separate room on a 16:8 light/dim light schedule (DM; 150 lx/5 lx). Both the bright and dim lights were typical fluorescent bulbs of the same wavelength. In both conditions, the bright lights were illuminated at 23:00 h. All experimental procedures were approved by The Ohio State University Institutional Animal Care and Use Committee.

2.2. Experimental design

After 8 weeks in lighting conditions, hamsters were tested for depression- and anxiety-like behaviors. Behavioral testing was performed between 08:00 and 12:00 and hamsters were allowed to habituate to the test room 30 min prior to testing. Tests were performed in the following order: (1) elevated-plus maze, (2) forced swim test, (3) sucrose anhedonia. Our experience with these tests at The Ohio State University Behavioral Phenotyping Center indicates no test order effects on these behavioral assessments. A baseline blood sample was taken after 4 weeks in lighting conditions and a terminal blood sample and brains were collected after 11 weeks (1 week after the conclusion of behavioral testing).

2.3. Behavioral tests

To assess depression-like behavioral responses in the forced swim test (Porsolt et al., 1977), hamsters were placed in a 4 L glass beaker filled with room-temperature water (22 ± 1 °C) inside an opaque cylindrical tank for 7 min. Behavior was recorded on video and subsequently scored with Observer software (Noldus, Wageningen, The Netherlands) by an observer unaware of assignment to experimental groups. The behaviors scored were: (1) climbing (i.e., vigorous swimming or scratching directed at the wall of the tank), (2) swimming (i.e., horizontal movement in the tank), and (3) floating/immobility (i.e., minimal movement necessary to keep head elevated above water surface).

Sucrose intake was determined by measuring consumption of a 1% sucrose solution over 24 h. To acclimate the animals to the novel solution, hamsters were presented with a bottle containing normal drinking water and the bottle containing sucrose solution over the weekend and left undisturbed for three days. On the fourth day each bottle was weighed, replaced in the cage, and then subsequently weighed again 24 h later. To control for possible side preferences, placement of the bottles in the cage was counterbalanced.

Anxiety-like behavior was tested in the elevated plus maze, which is a plus-shaped apparatus, elevated above the floor with two dark enclosed arms and two open (i.e.,

anxiogenic) arms. Each hamster was placed in the center of the test apparatus to begin and behavior was recorded on video for 5 min. An uninformed observer later scored videotapes for percent time spent in the open arms of the maze using Observer software.

2.4. Cortisol assays

After 4 weeks in experimental lighting conditions and at the conclusion of the study (11 weeks), blood samples were collected through heparinized capillary tubes from the retro-orbital sinus for radioimmunoassay (RIA) of cortisol concentrations. Samples were immediately centrifuged at 4 °C for 30 min at 3300 × *g* and plasma aliquots were stored at −80 °C until assayed. Total plasma cortisol concentrations 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. The intra-assay coefficient of variation was <10%. All procedures were performed in accordance with the manufacturer guidelines.

2.5. Analysis of hippocampal morphology

All hamsters were deeply anesthetized with isoflurane vapor and rapidly decapitated on the same day between 10:00 and 12:00 h. Brains were quickly dissected and processed for Golgi-Cox staining using a Rapid GolgiStain Kit (FD NeuroTechnologies). Briefly, whole brains were submerged in Golgi-Cox solution and stored for 14 days in the dark, followed by a 30% sucrose solution for 4 days. Brains were then rapidly frozen and 100 μm coronal sections were sliced on a cryostat and collected onto gelatin-coated glass slides. The stain was developed in NH_4OH for 10 min and sections were counterstained with cresyl violet. Finally, slides were dehydrated through a series of graded ethanol washes, cleared with xylene, coverslipped with Permount, and dried in the dark for at least 1 week.

Neurons impregnated with the Golgi-Cox solution were chosen within the CA1, CA3, and dentate gyrus (DG) regions of the hippocampus. Only neurons that were fully impregnated, not obscured by neighboring neurons, and had no obviously truncated dendrites were chosen for analysis. For each animal, six randomly chosen, representative neurons from different sections were completely traced at 20× (N.A. 0.75) using Neurolucida 8 software (MicroBrightField, Williston, VT, USA) for PC and a Nikon Eclipse E800 brightfield microscope. Dendritic spines were traced in each neuron at 100× (N.A. 1.30) in 4 apical and 4 basilar randomly chosen, representative dendrite segments of at least 20 μm in length, and at least 50 μm distal to the cell body. Morphological characteristics were analyzed using Neurolucida Explorer software (MicroBrightField, Williston, VT, USA) and consisted of: (1) dendritic length, (2) cell body area, (3) cell body perimeter, and (4) dendritic spine density.

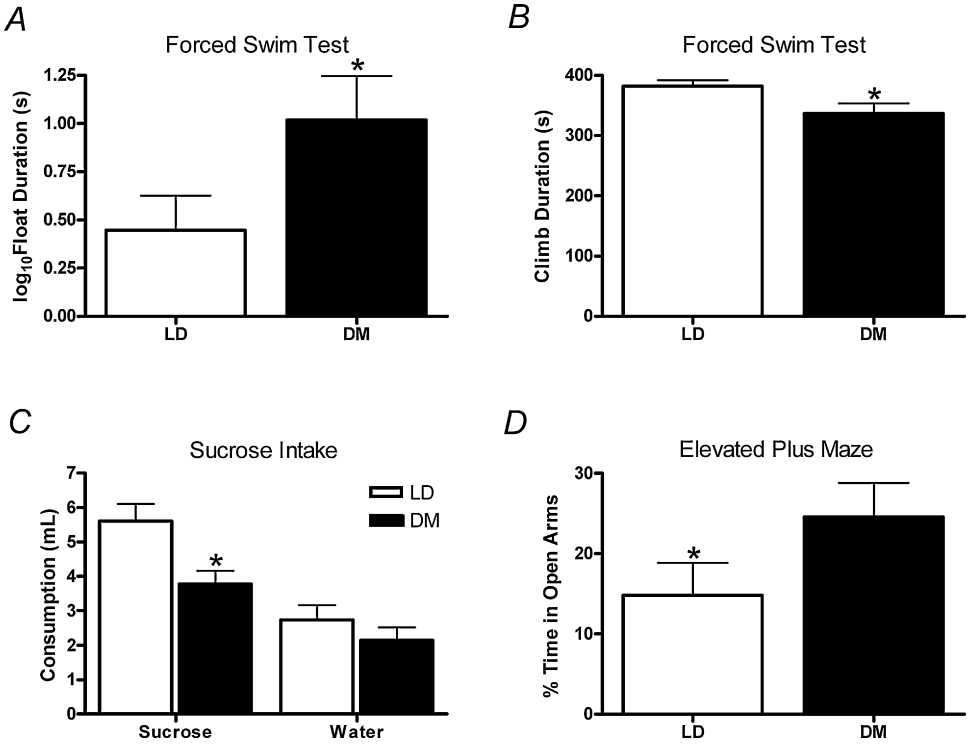

Figure 1 Depression- and anxiety-like behaviors in the forced swim test (A and B), sucrose intake test (C), and elevated plus maze (D). Hamsters exposed to dim light at night (DM-hamsters) spent more time engaged in immobility, or behavioral despair, in the forced swim test (A) and less time climbing to escape (B) compared with control (LD-hamsters). DM-hamsters consumed less sucrose solution in a test of sucrose intake, a behavioral measure of anhedonia, whereas water consumption was equivalent between groups (C). DM-hamsters reduced anxiety in the elevated plus maze and spent a greater percent time in the open arms than LD-hamsters (D). Graphs depict mean ± SEM. *$p < 0.05$.

2.6. Statistical analyses

Behavioral data from the forced swim test and elevated plus maze, as well as data from cortisol RIA and neuronal traces, were compared for group differences (LD vs. DM) using unpaired Student's *t*-tests. One animal died during the course of the study. In the case of immobility in the forced swim test, data were log transformed prior to analyses due to inequality of variances and one outlier was removed. Sucrose intake data was analyzed using two-way ANOVA with lighting condition (LD vs. DM) and liquid (water vs. sucrose solution) as the independent variables. Main effects were followed up with Fisher's exact test for post hoc comparisons. Correlations between depression-like behaviors and dendritic spine density were also calculated. Statistics were performed using Statview 5.0.1 for Windows. Mean differences were considered statistically significant when p was <0.05.

3. Results

3.1. Depression- and anxiety-like behaviors

Depression- and anxiety-like responses were observed in DM- vs. LD-hamsters using three different behavioral assays

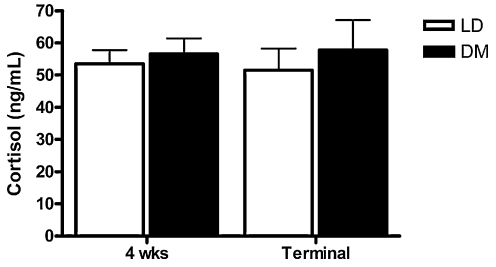

Figure 2 Baseline plasma cortisol concentrations at 4 weeks and 11 weeks (terminal) of experimental light cycles. There was no effect of light condition on cortisol concentrations, nor an effect of the duration of time spent in the condition (i.e., 4 week vs. 11 week).

(Fig. 1). In the forced swim test, DM-hamsters spent more time immobile ($t_{14} = 1.969$, $p < 0.05$; Fig. 1A) and less time climbing to escape ($t_{14} = -2.329$, $p < 0.05$; Fig. 1B) compared to LD-hamsters, indicating a depression-like phenotype. Furthermore, in a test of sucrose intake, two-way ANOVA revealed a main effect of lighting treatment ($F_{1,28} = 8.319$, $p < 0.01$), and post hoc tests revealed that DM-hamsters consumed less sucrose solution than LD-hamsters ($p < 0.01$; Fig. 1C), supporting the notion of an anhe-

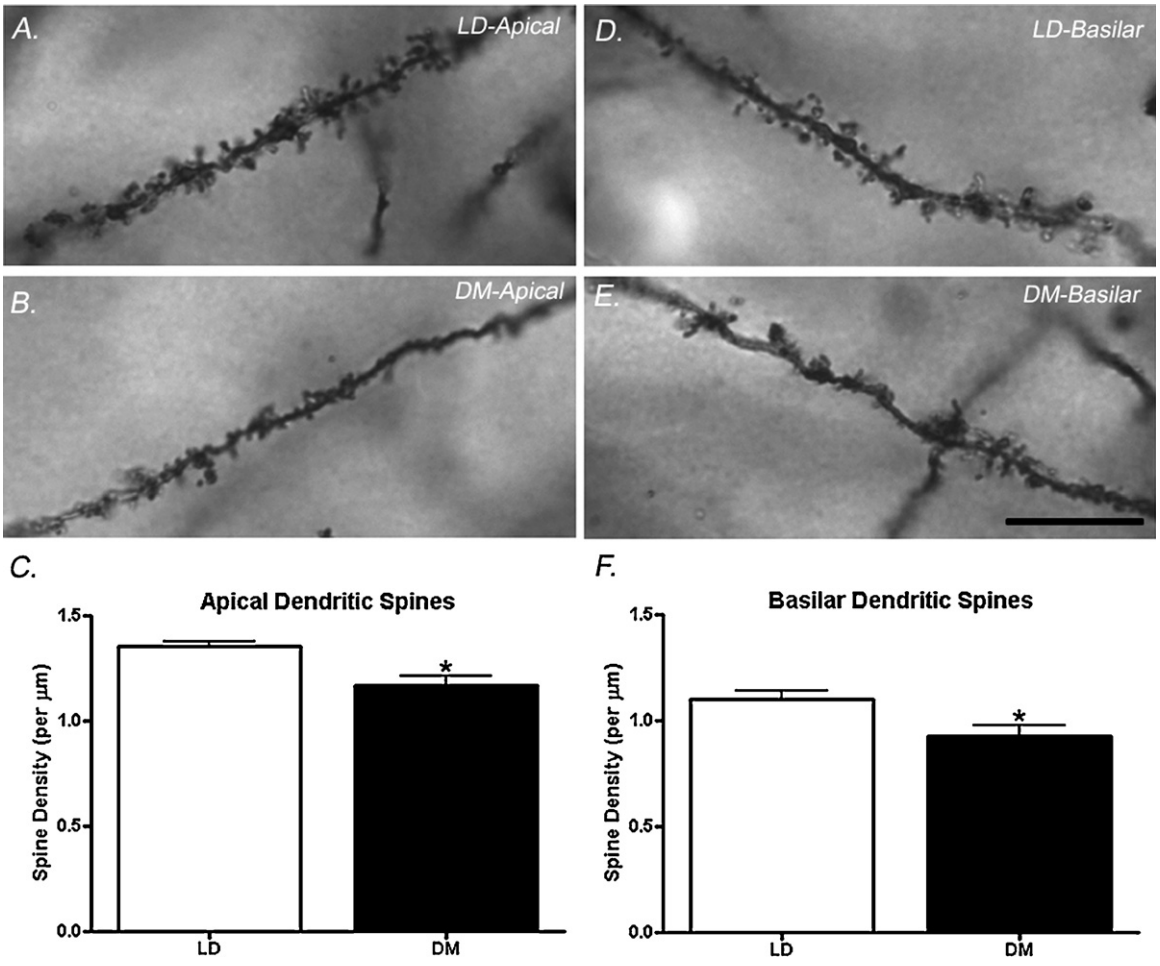

Figure 3 Dendritic spine density on apical and basilar dendrites in the CA1 region of the hippocampus. Hamsters exposed to dim light at night (DM-hamsters) significantly reduced dendritic spine density on both apical (A—C) and basilar (D—F) dendrites. Graphs depict mean ± SEM. *$p < 0.05$.

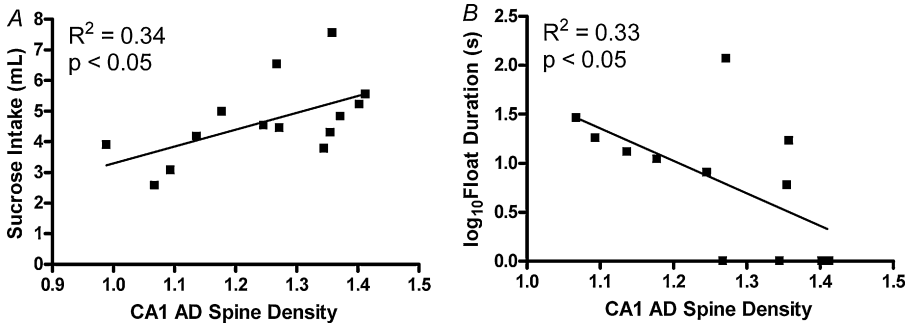

Figure 4 Correlations of depression-like behaviors and CA1 apical dendritic spine density. Sucrose intake positively correlated with spine density on CA1 apical dendrites such that less consumption (i.e., high anhedonic symptoms) correlated with reduced spine density (A). Immobility in the forced swim test negatively correlated with apical dendritic spine density in CA1 such that more float time (i.e., high behavioral despair) correlated with reduced spine density (B).

donic-like state in DM-hamsters. Water intake was equivalent between groups ($p > 0.05$). In contrast, DM-hamsters demonstrated less anxiety-like behavior in the elevated plus maze, as they spent greater percent time in the anxiogenic open arms of the maze compared with LD-hamsters ($t_{12} = 2.232$, $p < 0.05$; Fig. 1D).

3.2. Cortisol concentrations

Plasma cortisol concentrations were determined during the light phase after 4 and 11 weeks in LD vs. DM conditions (Fig. 2). There were no group differences in cortisol concentrations after 4 weeks in lighting conditions, nor at the conclusion of behavioral testing ($p > 0.05$; Fig. 2). Moreover, the duration of exposure to light at night also did not change cortisol concentrations, as there were no differences between the 4th week and 11th week samples ($p > 0.05$).

3.3. Hippocampal cell morphology

Hippocampal neurons from CA1, CA3 and DG were traced and analyzed for morphological characteristics (Fig. 3). Two brains were lost due to crumbling during the sectioning process and one animal died during the course of the study, so $N = 6$ LD and $N = 8$ DM brains in total were used for morphological analyses. In the CA1 region, DM-hamsters had significantly reduced dendritic spine density in both apical ($t_{12} = -3.465$, $p < 0.01$; Fig. 3C) and basilar ($t_{12} = -2.708$, $p < 0.05$; Fig. 3F) dendrites. The reduction in spine density on CA1 apical dendrites significantly correlated with immobility in the forced swim test ($r = -0.578$, $p < 0.05$; Fig. 4A) and sucrose intake ($r = 0.581$, $p < 0.05$; Fig. 4B). DM- and LD-hamsters did not differ in any other measures of cell morphology in CA1 and no differences were observed in CA3 or the DG ($p > 0.05$ for all comparisons; Table 1).

4. Discussion

Exposure to dim light at night is sufficient to provoke a depression-like phenotype in ovariectomized female hamsters, as well as low anxiety-like responses. In addition, dim light at night reduces the density of dendritic spines, the primary sites of synaptic contacts, in hippocampal CA1 pyramidal cells. These changes were observed independently of changes in baseline plasma cortisol concentrations. Other measures of neuronal plasticity, such as changes in dendritic length and cell body size, were not observed, suggesting that light at night specifically affects the connectivity of hippocampal neurons rather than cell size or other aspects of morphology. Moreover, the density of CA1 dendritic spines significantly correlated with depression-like behaviors in both behavioral assays, suggesting a functional relationship.

Table 1 Morphological characteristics of hippocampal CA1, CA3, and dentate gyrus (DG) neurons represented as mean micrometers ± SEM. AD — apical dendrite; BD — basilar dendrite.

	Apical dendrite length	Basilar dendrite length	AD spine density	BD spine density	Cell body perimeter	Cell body area
CA1						
LD	1451.0 ± 92.9	1161.2 ± 52.2	see Fig. 3	see Fig. 3	66.7 ± 2.0	269.8 ± 9.6
DM	1467.7 ± 126.3	1099.6 ± 103.6	see Fig. 3	see Fig. 3	72.4 ± 2.8	295.7 ± 21.1
CA3						
LD	1227.8 ± 91.0	1155.5 ± 72.1	0.94 ± 0.12	0.89 ± 0.12	85.4 ± 2.7	420.8 ± 15.2
DM	1272.3 ± 118.3	1214.9 ± 99.0	0.88 ± 0.03	0.91 ± 0.04	86.3 ± 5.1	399.4 ± 22.5
DG						
LD	1020.0 ± 55.9	n/a	0.96 ± 0.05	n/a	69.8 ± 3.7	277.9 ± 26.2
DM	1275.0 ± 111.5	n/a	1.06 ± 0.05	n/a	76.4 ± 2.6	335.3 ± 24.6

Data represent mean ± SEM.

4.1. Behavior differences

Hamsters chronically exposed to dim light at night exhibited more immobility, generally interpreted as behavioral despair (Porsolt et al., 1977), in the forced swim test and consumed less sucrose solution in a test of sucrose intake, which is interpreted as an anhedonic-like response (Willner et al., 1992). Taken together, these behavioral responses suggest a depression-like state. DM-hamsters also spent more time in the open arms of the elevated plus maze, indicating a reduced anxiety-like response. These results are consistent with our previous observation that constant bright light provokes a depression-like phenotype and reduced anxiety in male mice (Fonken et al., 2009). One possible explanation for the findings is that dim light at night is stressful and alters baseline circulating glucocorticoid concentrations, which may in turn influence behavior. This possibility can be ruled out because cortisol concentrations were equivalent between groups both after 4 weeks in lighting conditions and at the conclusion of the study. In addition, exposure to dim light at night does not alter diurnal rhythms of corticosterone in mice (Fonken et al., 2010). Further studies, however, will be necessary to confirm this in Siberian hamsters.

The observation of increased depression-like behavior in coincidence with attenuated anxiety is unexpected, given that depression and anxiety are often comorbid in humans (Fawcett and Kravitz, 1983). It is possible that, in our model, the elevated plus maze is more reflective of a novelty-seeking or impulsive aspect of the phenotype rather than anxiety per se. In this case, DM-hamsters may be displaying a phenotype more reminiscent of depressive subtypes which coincide with impulsive risk-taking behavior, such as substance abuse disorders or suicide attempts. Indeed, some studies regarding rodent chronic stress models have shown anhedonia to coexist with heightened novelty-seeking behavior (Shumake et al., 2005; Li et al., 2010a,b); however, further behavioral testing is necessary to either support or refute these relations in our model.

It is important to note that we have previously shown no differences in 24-h activity patterns or total daily activity of animals chronically exposed to dim light at night compared to those housed in a standard light—dark cycle (Fonken et al., 2010). Therefore, despite the activity-dependent nature of two of our behavioral measures, the present findings are unlikely to be confounded by alterations in circadian rhythms of activity or amount of activity.

Although the precise mechanism underlying the link between light at night and mood remains to be specified, one putative mechanism could be via suppression of pineal melatonin. Temporal organization of physiological processes relies largely on light information being transduced into a hormonal signal and circulated throughout the body. During the day, light is received by the photoreceptive retinal ganglion cells of the eye and then transmitted via the retinohypothalamic tract to the suprachiasmatic nuclei (SCN), the master circadian pacemaker. The SCN controls production and secretion of the pineal hormone, melatonin, which is secreted into the bloodstream only during the night, making it a useful physiological cue for nighttime (Reiter, 1993). However, exposure to light at night robustly suppresses melatonin secretion, thus distorting the body's time of day information (Navara and Nelson, 2007). In our study, 5 lx dim light at night was likely sufficient to suppress melatonin; illumination levels as low as 1.08 lx inhibit pineal melatonin production in Syrian hamsters (Brainard et al., 1982).

Melatonin may play a role in mood. Agomelatine, a melatonin-receptor agonist which also antagonizes serotonin (5-HT_{2c}) receptors, is an effective anti-depressant (Goodwin et al., 2009; Kennedy and Rizvi, 2010). Furthermore, melatonin itself has immunomodulatory effects on neuroinflammation (Maldonado et al., 2009), as well as the ability to re-entrain disrupted circadian rhythms (Pandi-Perumal et al., 2006), both potential anti-depressive mechanisms. Given this link between melatonin and depression, as well as the melatonin-suppressing effect of light at night, it is plausible that the observed behavioral changes may occur as a direct result of melatonin suppression. Future studies will determine whether the reported effects are reversible by returning hamsters to standard light—dark exposure after chronic light at night, and by directly manipulating melatonin to determine whether there exists a causative link with the presently reported findings.

4.2. Hippocampal plasticity

A large literature demonstrates the morphological changes that hippocampal pyramidal cells undergo when exposed to stress and glucocorticoids (for review: McEwen, 2008). However, to the best of our knowledge, this is the first study to document light at night as a sufficient stimulus to induce changes in hippocampal plasticity in the absence of baseline changes in cortisol. We measured dendritic spine density on segments at least 50 μm from the cell body, thus targeting our analysis to the primary sites of excitatory neuronal input (Megias et al., 2001; von Bohlen Und Halbach, 2009). Therefore, our observation that dim light at night reduces dendritic spine density is likely reflective of reduced excitatory input to hippocampal CA1 pyramidal cells. It is noteworthy that dendritic spine morphology relays information about the strength and maturity of the spine and associated synapse (Yoshihara et al., 2009); however, in the present study we measured density of total spines and did not distinguish between morphological classifications of spines. This is an interesting area that requires future study.

The observation that these changes correlate with the depressive behavioral responses suggests a functional role of decreased CA1 spine density in depressive affect induced by light at night. In support of this, studies show that in female rodents, reduced spine density in the hippocampus correlates with learned helplessness (Hajszan et al., 2010). Hippocampal spine density has also been linked to several neuropsychiatric disorders, and particularly depression via the neurotrophic hypothesis, which suggests that depressive pathology involves altered plasticity of neuronal pathways (reviewed in: Altar, 1999). Reduced spine density has been associated with major depression in humans (Law et al., 2004) and antidepressant treatment increases CA1 spine density in rats (Hajszan et al., 2005; Norrholm and Ouimet, 2001). Antidepressant treatment also increases brain-derived neurotrophic factor (BDNF) mRNA in rat brain (Altar, 1999). Putatively, insufficient neurotrophic support in depressive disorders could cause structural disorganization in the brain (Angelucci et al., 2005). Rapid changes in spine density in other brain regions, such as prefrontal cortex, have

also been implicated in depression (Li et al., 2010a). We restricted our analysis to the hippocampus after chronic light treatment in our study, but future studies could investigate structural changes to the prefrontal cortex, as well as the rapidity of these changes.

The mechanism of reduced CA1 dendritic spine density in DM-hamsters likely involves suppression of pineal melatonin production. Melatonin ameliorates corticosterone-induced reduction of spines in the hippocampus of male mice (Crupi et al., 2010) and increases hippocampal neurogenesis (Ramirez-Rodriguez et al., 2009), thus an insufficiency of melatonin in DM-hamsters may underlie our observations. Estradiol increases hippocampus dendritic spine density (Woolley and McEwen, 1992), but we avoided this potential confound in the current study by ovariectomy. On the basis of results obtained in this study, current work in our laboratory is aimed at elucidating the exact role of melatonin in the current findings, as well as determining whether female steroid hormones and light at night may interact to influence hippocampal plasticity. In contrast, however, CA3 and DG neurons failed to show any morphological changes in response to dim light at night. CA3 neurons are generally resistant to remodeling in response to stress in female rodents compared to males (Galea et al., 1997). A similar effect of sex could account for our finding that CA3 and DG neurons were more resistant to change in response to dim light at night than neurons in CA1.

In conclusion, over the past century exposure to nighttime illumination and the incidence of depressive disorders have increased in tandem, yet there has been little research into a possible connection, despite increasing evidence of the antidepressant and neuroprotective actions of melatonin. Here we demonstrate that dim light at night is sufficient to provoke depression-like behaviors, which correlate with reduced density of CA1 dendritic spines in the hippocampus of female hamsters. These findings warrant further research into light at night as a putative environmental contributor to depressive disorders.

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Conflict of interest

The authors of the current study have no conflicts of interest that would inappropriately influence, or be perceived to influence, their work.

Contributors

TAB and RJN designed the study. TAB, LKF, JCW performed the experiments and analyzed the results. TAB, AH, and RJN wrote the paper.

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