

Chronic Citalopram Treatment Ameliorates Depressive Behavior Associated With Light at Night

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Chronic exposure to light at night (LAN) is a circadian disruptor and may be linked to various health risks, including mood disorders. We recently demonstrated that chronic exposure to dim (5 lux) LAN provokes depressive-like behaviors and reduced hippocampal CA1 dendritic spine density in female hamsters. Whether this model is responsive to selective serotonin reuptake inhibitors remains unspecified. In this study, we exposed hamsters to 5 lux LAN and treated with citalopram to determine effects on depressive-like behavior and CA1 dendritic spine density. Female hamsters were ovariectomized at adulthood and housed in either a standard light–dark cycle (LD) or dim LAN (dLAN). After 4 weeks exposure, treatment with either citalopram or vehicle was administered for 2 weeks while hamsters remained in experimental lighting conditions. Depressive-like behavior was assayed using the forced swim test and brains were processed for Golgi-Cox staining and analyzed for dendritic spine density. Treatment with citalopram rescued behavior in the forced swim test in hamsters housed in dLAN, but had no effect on hamsters housed in LD. Dendritic spine density in CA1 was moderately improved by citalopram treatment, but not fully restored. These results validate our LAN paradigm as a depression model by showing citalopram selectively improves depressive-like behavior in dLAN conditions, but not in LD conditions. These data also suggest standard SSRI therapy may be effective for individuals experiencing depression related to circadian disruption and LAN exposure, such as shift workers.

Keywords: light pollution, hippocampus, *Phodopus sungorus*, SSRI, circadian

Exposure to light at night (LAN) is a relatively new phenomenon in human history, having arisen only since the widespread adoption of the electric light bulb about 120 years ago. LAN has allowed humans to cultivate 24-hr societies; 99% of individuals living in the U.S. or Europe experience nightly light pollution (Navara & Nelson, 2007) and about 20% of workers in any urban economy work night shifts (Rajaratnam & Arendt, 2001). LAN appears to disrupt circadian organization either by suppression of pineal melatonin secretion, or inappropriate phase relationships among various molecular, cellular, and physiological responses. Pineal melatonin production occurs during the night in both diurnal and nocturnal species; exposure to light robustly suppresses its secretion. Dysregulation of the daily melatonin rhythm distorts the body's time of day information, which could lead to disruptions in circadian clock gene expression and hormone secretion (Stehle, von Gall, & Korf, 2003), which have been linked to mood (Bunney & Bunney, 2000). Shift workers and individuals exposed to disruptive LAN are at increased risk of mood disorders (Driesen, Jansen, Kant, Mohren, & van Amelsvoort, 2010; Meyrer, Demling, Kornhuber, & Nowak, 2009; Rajaratnam et al., 2011; Rosenberg & Doghramji, 2011), but the precise mechanism linking LAN to mood remains unspecified.

The hippocampus is one brain structure involved in the pathophysiology of major depression. Depressed individuals show characteristic hippocampal atrophy (Frodl et al., 2002; Sheline, Sanghavi, Mintun, & Gado, 1999), and depression symptoms have been linked to reductions in the complexity of hippocampal neurons, including reduced numbers of dendritic spines (Hajszan et al., 2009; Hajszan, MacLusky, & Leranth, 2005; Hajszan et al., 2010). Antidepressant treatment with a selective serotonin reuptake inhibitor (SSRI) ameliorates dendritic spine deficits in rats (Hajszan et al., 2005). Melatonin receptors are present in the rodent hippocampus and melatonin itself modulates neuronal excitability in the hippocampus (Musshoff, Riewenherm, Berger, Fauteck, & Speckmann, 2002). Furthermore, melatonin administration prevents the depressive-like behavior and reduction in hippocampal neuron complexity observed under a chronic stress paradigm (Crupi et al., 2010). These observations make the hippocampus an interesting target for studies in our model.

Citalopram is a selective serotonin reuptake inhibitor with high selectivity for the serotonin transporter over other transporter proteins. It is an effective and commonly prescribed treatment for depression, but distinct from other pharmacotherapeutics in its class because it also has linear pharmacokinetics (Keller, 2000). Evidence suggests citalopram does not affect spontaneous locomotor activity in rodents (Cervo et al., 2005), making it an attractive choice for behavioral studies. Whether SSRI treatment is effective for treating depression specifically related to circadian disruption by exposure to LAN, however, remains unknown.

We recently demonstrated that chronic exposure to dim LAN (dLAN) provokes depressive-like behaviors in ovariectomized female hamsters and reduced the number of dendritic spines on

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hippocampus CA1 pyramidal neurons (Bedrosian, Fonken, Walton, Haim, & Nelson, 2011). Hamsters were ovariectomized in order to prevent any confounding effects of fluctuating estrogen levels on hippocampal morphology (Woolley & McEwen, 1992). The effect of chronic SSRI treatment in this model has remained unspecified. In order to investigate this question, we hypothesized that 2 weeks treatment with citalopram would improve depressive-like behavior and the reduction in dendritic spine density observed under LAN.

Method

Animals

Forty adult female Siberian hamsters (*Phodopus sungorus*) were obtained from our breeding colony at The Ohio State University. This species is nocturnal and exhibits a robust nightly melatonin rhythm. 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 $50 \pm 5\%$. Food (Harlan Teklad 8640, Indianapolis, IN) 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 1 week. Following the recovery period, hamsters were maintained in either control (N = 20) or experimental (N = 20) lighting conditions as described below. The control condition was the same as the standard colony room, which was a 16:8 light/dark cycle (150 lux/0 lux), and the experimental condition was a 16:8 light/dim light cycle (150 lux/5 lux). Both the bright and dim lights were typical “cool white” fluorescent bulbs. In both conditions, the bright lights were illuminated at 22:00 hr. All experimental procedures were approved by The Ohio State University Institutional Animal Care and Use Committee.

Drug Administration

After 4 weeks in experimental lighting conditions, citalopram (0.16g/L) was administered in the drinking water with 1% saccharin to mask any taste of the drug, according to previous studies (Warner-Schmidt et al., 2011; Warner-Schmidt et al., 2011). Control groups (N = 10 from each lighting condition) drank 1% saccharin solution. Chronic treatment lasted 18 days and behavioral testing and tissue collection occurred during the last 4 days of treatment. Water consumption was measured twice weekly. Hamsters remained in experimental lighting conditions throughout the duration of the study.

Forced Swim Test

To assess depression-like behavioral responses in the forced swim test (Porsolt, Bertin, & Jalfre, 1977), hamsters were placed in an opaque cylindrical tank filled with room-temperature water (22 ± 1 °C) for 10 min. Behavior was recorded on video and the full 10 min of test time was subsequently scored with Observer software (Noldus, Wageningen, The Netherlands) by an observer unaware of assignment to experimental groups. The behaviors scored were: (a) climbing (i.e., vigorous swimming or scratching directed at the wall of the tank); (b) swimming (i.e., horizontal

movement in the tank); and (c) floating/immobility (i.e., minimal movement necessary to keep head elevated above water surface).

Analysis of Hippocampal Morphology

Hamsters were deeply anesthetized with isoflurane vapors and rapidly decapitated between 10:00 a.m. and 12:00 p.m. a day after the conclusion of behavior testing. Brains were quickly removed and 20 brains were randomly chosen to be processed for Golgi-Cox staining using a Rapid GolgiStain Kit (FD NeuroTechnologies) as previously described (Bedrosian et al., 2011). Briefly, 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 μ m 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 region of the hippocampus based on our previously observed differences in this region. Only neurons that were fully impregnated, not obscured by neighboring neurons, and had no obviously truncated dendrites were chosen for analysis. For each animal, 4–6 randomly chosen, representative neurons from different sections were chosen. Dendritic spines were traced in each neuron at 100x (N.A. 1.30) in four apical and four basilar randomly chosen, representative dendrite segments of at least 20 μ m in length, and at least 50 μ m distal to the cell body, using NeuroLucida 8 software (MicroBrightField, Williston, VT) for PC and a Nikon Eclipse E800 brightfield microscope. Dendritic spine density was analyzed using NeuroLucida Explorer software (MicroBrightField, Williston, VT).

Statistical Analyses

Water consumption was compared for each day using one-way ANOVA with treatment (vehicle vs. citalopram) as the independent variable. Behavior and brain morphology data were analyzed using two-way ANOVA with lighting condition (LD vs. dLAN) and drug treatment (vehicle vs. citalopram) as the independent variables. Main effects were followed up with Fisher's post hoc comparisons. Statistics were performed using Statview 5.0.1 for Windows PC. Mean differences were considered statistically significant when $p \leq .05$.

Results

Water Consumption

Water intake was sampled twice weekly throughout the 2 weeks of citalopram treatment by weighing bottles at baseline and then again 24 hr later. Over the first 24 hr of treatment, hamsters receiving citalopram in the water consumed less than hamsters receiving vehicle only ($F_{1,37} = 14.46, p < .05$). At all subsequent sampling dates, however, hamsters consumed equivalent amounts of water regardless of treatment ($p > .05$ in all cases), averaging approximately 4 ml per day (see Figure 1).

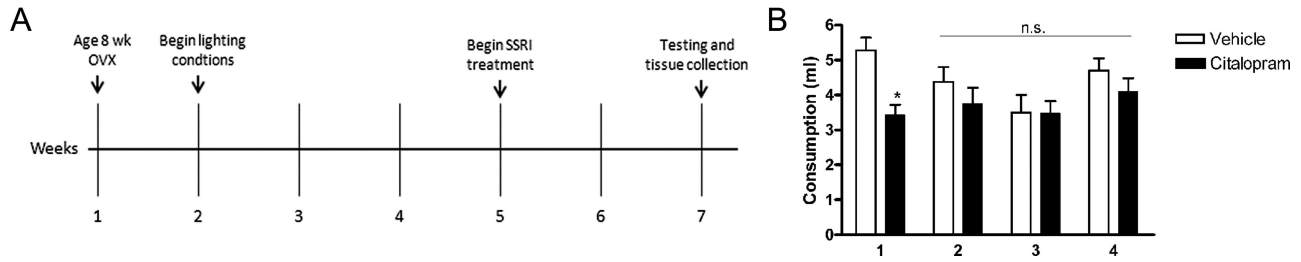


Figure 1. Experimental timeline for treatment and testing (A). Water consumption sampled four times throughout the two weeks of treatment differed only during the first 24 hr in citalopram vs. vehicle groups (B). OVX: ovariectomy; * $p < 0.05$ vehicle vs. citalopram, day 1.

Depression-Like Behavior

Hamsters were tested for depressive-like behaviors in the forced swim test by assessing time spent climbing versus immobile and latency to float. Hamsters housed in LD spent more time in escape-directed behavior (i.e., climbing) compared to hamsters housed in dLAN ($F_{1,33} = 5.052, p < .05$). There was also a main effect of treatment ($F_{1,33} = 4.177, p < .05$). As a planned comparison, we found that citalopram-treated hamsters in dLAN spent a greater duration climbing compared to vehicle-treated hamsters in dLAN (post hoc, $p < .05$; **Figure 2A**). Immobility, generally interpreted as behavioral despair in this test, was increased in hamsters housed in dLAN ($F_{1,33} = 4.826, p < .05$). There was also an effect of treatment ($F_{1,33} = 4.300, p < .05$) and a light \times treatment interaction effect ($F_{1,33} = 4.856, p < .05$). Citalopram-treated hamsters in dLAN spent less time immobile than vehicle-treated hamsters in dLAN (post hoc, $p < .05$; **Figure 2B**). Furthermore, latency to first become immobile was reduced in hamsters in dLAN ($F_{1,33} = 17.720, p < .05$) with an effect of treatment ($F_{1,33} = 9.277, p < .05$) and a light \times treatment interaction ($F_{1,33} = 8.261, p < .05$). Citalopram-treated hamsters in dLAN had a greater latency to float compared to vehicle-treated hamsters in dLAN (post hoc, $p < .05$; **Figure 2C**).

Hippocampal Morphology

Dendritic spine density on hippocampal CA1 pyramidal neurons was reduced in dLAN compared to LD on both apical ($F_{1,15} = 6.781, p < .05$) and basilar ($F_{1,15} = 8.899, p < .05$) dendrites, without an effect of citalopram treatment (**Figure 3A–B**). Planned comparison post hoc analyses after the light effect, however,

revealed a subtle distinction. Vehicle-treated hamsters in LD versus dLAN had significantly different levels of spine density (post hoc, $p < .05$), whereas citalopram-treated hamsters in dLAN were not significantly different from either LD or dLAN vehicle-treated groups, suggesting a slight improvement with treatment.

Discussion

Exposure to artificial LAN has grown in prevalence during the past 100 years, which has allowed humans to stray from natural day-night cycles, potentially provoking circadian dysregulation and changes in physiology and behavior. Our previous studies have shown that LAN provokes depressive-like behavior in rodents (Bedrosian et al., 2012; Bedrosian et al., 2011; Fonken et al., 2009). The response of this phenomenon to an SSRI, the standard in depression treatment, has remained unknown. In this study, we demonstrate for the first time that the selective serotonin reuptake inhibitor, citalopram, prevents the expression of depressive-like behaviors in the forced swim test after chronic LAN exposure, without affecting nondepressed hamsters housed without LAN. Citalopram did not, however, fully restore hippocampal dendritic spine density after LAN exposure. This study suggests that our LAN paradigm can serve as a depression model in which antidepressant treatment is selectively effective in hamsters showing depressive-like behavior.

Citalopram is a selective serotonin reuptake inhibitor with high selectivity for 5-HT over other transmitters. Citalopram inhibits uptake of 5-HT 3,400 times more potently than of norepinephrine and 22,000 times more potently than of dopamine, making it more selective than many other SSRIs, including fluoxetine, paroxetine,

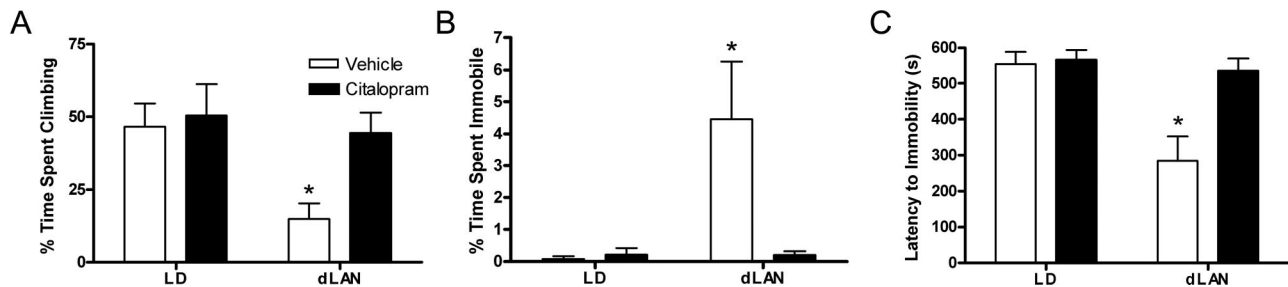


Figure 2. Depressive-like response. Hamsters housed in dLAN spent less time climbing in the forced swim test, but citalopram treatment ameliorated this deficit (A). dLAN hamsters also spent more time immobile, but citalopram treatment reduced floating to LD levels (B). Latency to immobility was reduced in dLAN hamsters, but was enhanced with citalopram (C). * $p < 0.05$ post-hoc, dLAN vehicle vs. each other group.

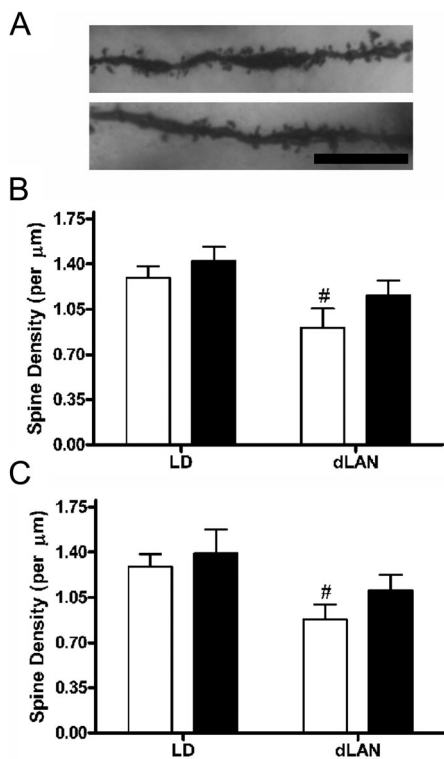


Figure 3. Hippocampus dendritic spine morphology. Representative photomicrographs of apical dendritic spines in LD (top) and dLAN (bottom) in CA1 (A). CA1 dendritic spine density was reduced in hamsters housed in dLAN on both apical (B) and basilar (C) dendrites. Spine density on citalopram-treated hamsters in dLAN was not significantly different from either LD or dLAN vehicle-treated groups, suggesting a slight improvement with treatment. # $p < 0.05$ planned comparisons between vehicle groups.

and sertraline (Keller, 2000). We chose citalopram because it is an effective and commonly prescribed treatment for depression, but distinct from other pharmacotherapeutics in its class because it also has linear pharmacokinetics (Keller, 2000). Evidence suggests citalopram does not affect spontaneous locomotor activity in rodents (Cervo et al., 2005), and thus would not bias our results from the forced swim test. This notion is further supported by the finding that citalopram did not affect forced swim test behavior in hamsters housed in LD.

SSRI treatment promotes dendritic complexity of hippocampal neurons and formation of pyramidal dendritic spine synapses (Banar, Dwyer, & Duman, 2011; Bessa et al., 2009; Hajszan et al., 2005). Dendritic spines are highly plastic structures, capable of changing within minutes in response to certain environmental stimuli (Fischer, Kaech, Knutti, & Matus, 1998). In this study, dLAN reduced the number of dendritic spines on both apical and basilar dendrites of CA1 pyramidal neurons. Because we targeted our analysis to dendritic segments at least 50 μm from the cell body, we restricted our analysis to the primary sites of excitatory neuronal input (Megias, Emri, Freund, & Gulyas, 2001; von Bohlen Und Halbach, 2009). Thus, our results may reflect diminished excitatory input to CA1 pyramidal neurons in LAN. Under

the dLAN conditions tested in this experiment, only slight increases in CA1 dendritic spine density were observed with citalopram treatment, but not full recovery of LD levels. This may reflect other constraints on dendritic spine density or other factors, such as stress hormone concentrations or lack of melatonin, which cannot be overcome by SSRI treatment alone. Importantly, we measured overall spine numbers and did not distinguish between morphological classifications of spines in this study. Because morphology provides information about the strength and maturity of the spine and its associated synapse (Yoshihara, De Roo, & Muller, 2009) distinguishing by spine type is an interesting area for future investigation and may reveal more nuanced effects of citalopram treatment.

On a broader level, the upstream mechanism linking LAN to behavioral and neuronal changes remains unspecified. One possibility is that reduced melatonin secretion under LAN conditions provokes a cascade of downstream effects. Temporal organization of physiological processes relies largely on the transduction of light information into a hormonal signal that is circulated throughout the body. During the day, light received by the intrinsically photoreceptive retinal ganglion cells of the eye is transmitted via the retinohypothalamic tract to the suprachiasmatic nuclei (SCN). The SCN in turn regulates production and secretion of the pineal hormone, melatonin, which is secreted into the bloodstream during the dark, making it a useful physiological cue for nighttime (Reiter, 1993). Exposure to LAN, however, suppresses production of melatonin, thus distorting natural time of day information (Navara & Nelson, 2007). In this study, we used 5 lux LAN, that is likely sufficient to suppress melatonin levels. Light levels as low as 1.08 lux inhibit pineal melatonin production in Syrian hamsters (Brainard, Richardson, Petterborg, & Reiter, 1982). Importantly, melatonin has been implicated in mood. In rodents, melatonin administration prevents stress-induced depression-like behaviors and reductions in hippocampal dendritic complexity (Crupi et al., 2010).

Overall, the results of this study validate our LAN paradigm as a depression model in which depression-like behavior in dLAN is selectively improved by citalopram treatment, without any effect of the drug on hamsters in LD. This is the first study, to our knowledge, to validate the forced swim test using an SSRI in this particular species. The results also suggest that SSRI treatment may be equally effective for treating depression related to LAN, in populations such as shift workers, as for treating general major depression. Nonetheless, more attention should be given to LAN as a potential circadian disruptor with downstream effects on physiology and mood.

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