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Research article

Hypothalamic dopaminergic neurons in an animal model of seasonal affective disorder

Sean P. Deats [a], Widya Adidharma [a,b], Lily Yan [a,b,*]

[a] Department of Psychology, Michigan State University, East Lansing, MI 48824, USA
[b] Neuroscience Program, Michigan State University, East Lansing, MI 48824, USA

HIGHLIGHTS

- The number of hypothalamic DA and SST neurons were reduced following light deficiency.
- Blocking orexingergic signaling led to a reduction in the number of hypothalamic DA neurons.
- The number of hypothalamic SST neurons was not affected by orexinergic signaling.
- Light-dependent changes in the hypothalamic DA neurons are likely mediated by orexinergic pathways.

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ABSTRACT

Light has profound effects on mood regulation as exemplified in seasonal affective disorder (SAD) and the therapeutic benefits of light therapy. However, the underlying neural pathways through which light regulates mood are not well understood. Our previous work has developed the diurnal grass rat, *Arvicanthis niloticus*, as an animal model of SAD. Following housing conditions of either 12:12 h dim light:dark (DLD) or 8:16 h short photoperiod (SP), which mimic the lower light intensity or short day-length of winter, respectively, grass rats exhibit an increase in depression-like behavior compared to those housed in a 12:12 h bright light:dark (BLD) condition. Furthermore, we have shown that the orexinergic system is involved in mediating the effects of light on mood and anxiety. To explore other potential neural substrates involved in the depressive phenotype, the present study examined hypothalamic dopaminergic (DA) and somatostatin (SST) neurons in the brains of grass rats housed in DLD, SP and BLD. Using immunostaining for tyrosine hydroxylase (TH) and SST, we found that the number of TH- and SST-ir cells in the hypothalamus was significantly lower in the DLD and SP groups compared to the BLD group. We also found that treating BLD animals with a selective orexin receptor 1 (OX1R) antagonist SB-334867 significantly reduced the number of hypothalamic TH-ir cells. The present study suggests that the hypothalamic DA neurons are sensitive to daytime light deficiency and are regulated by an orexinergic pathway. The results support the hypothesis that the orexinergic pathways mediate the effects of light on other neuronal systems that collectively contribute to light-dependent changes in the affective state.

1. Introduction

Seasonal affective disorder (SAD) is a major depressive disorder that stems from the seasonal ebb and flow of daily light exposure [31]. SAD patients experience recurring episodes of depression and anxiety starting in the fall and winter when daylight is shorter and less bright. Their symptoms can be ameliorated by bright light therapy and remitted completely in spring and summer.

Several animal models have been developed to explore the neuropathology of SAD [11,16,25,26,29,30,36]. Compared to commonly used nocturnal species, diurnal models are proposed to be more advantageous in elucidating the neuropathology of SAD [3,15,37]. Using the diurnal Nile grass rats, we and others have observed depression- and anxiety-like behaviors in winter-like lighting conditions, i.e. short photoperiods [4,18] or daytime dim lighting [7,17]. Furthermore, we found that hypothalamic neurons containing the neuropeptide orexin are likely to play a role in mediating the

Abbreviations: BLD, bright light/dark; DLD, dim light/dark; ir, immunoreactive; LD, light/dark cycle; OXA, orexin-A peptide; OX1R, orexin-1 receptor; PaVN, paraventricular nucleus; PeVN, periventricular nucleus; SP, short photoperiod; SST, somatostatin; TH, tyrosine hydroxylase; ZT, Zeitgeber time.

* Corresponding author at: Department of Psychology & Neuroscience Program, 108 Giltner Hall, East Lansing, MI 48824, USA. Fax: +1 517 432 2744.
E-mail address: yanl@msu.edu (L. Yan).

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effects of light on mood and anxiety. In grass rats, orexin neurons show light-induced activation following acute light exposure [1], and also respond to chronic changes in lighting condition, such that daytime light deficiency leads to a reduction in the number of orexin-expressing neurons [7]. Additionally, treating grass rats housed in summer-like bright light conditions with a selective orexin receptor 1 (OX1R) antagonist induced depression- and anxiety-like behaviors [7]. These findings collectively suggest that the orexinergic pathways are involved in light-dependent changes in mood and anxiety.

The objective of the present study is to explore the potential downstream targets of the orexinergic pathways in light-dependent mood changes. A recent study using nocturnal Long Evans rats suggests that hypothalamic dopaminergic neurons are involved in light-dependent changes in affective states [9]. Housing Long Evans rats in long photoperiods induced a depression- and anxiety-like phenotype that was associated with a reduction of dopaminergic (DA) neurons and an increase in somatostatin (SST) neurons within the paraventricular (PaVN) and periventricular hypothalamic nuclei (PeVN). Furthermore, a chemical lesion of hypothalamic DA neurons in rats housed in neutral photoperiods led to depression- and anxiety-like behaviors. It is intriguing to consider that these groups of neurons may respond to ambient lighting conditions and to orexinergic inputs in a diurnal species. In the present study, we first assessed the effects of lighting conditions on hypothalamic DA and SST neurons in grass rats. We then tested if orexinergic pathways mediated these effects. The results provide insights into the neural mechanisms underlying light-dependent changes in mood and anxiety in a diurnal species, and contribute to a better understanding of the neuropathology of SAD.

2. Methods

2.1. Animals and housing conditions

Male grass rats (*Arvicanthis niloticus*) were produced from a breeding colony originally established with animals imported from sub-Saharan Africa in 1993 and maintained at Michigan State University [24]. The animals in the colony were housed in a 12 h light: 12 h dark (LD) cycle with food (Prolab 2000 #5P06, PMI Nutrition LLC, MO, USA) and water available *ad libitum*. The time of lights-on was defined as Zeitgeber time (ZT) 0. All procedures were conducted in accordance with the Michigan State University IACUC.

2.2. Experiment 1: effects of lighting conditions on hypothalamic TH-ir and SST-ir cells

Brains ($n = 6$/group) used in this experiment were obtained from two previous studies, in which animals were housed in either bright light: dark (BLD, 12:12 h LD, 1000 lux/1 lux), dim light: dark (DLD, 12:12 h LD, 50 lux/1 lux) or short photoperiod (SP, 8:16 h LD, 1000 lux/1 lux) for 4 weeks [17,18]. The animals were tested for depression-like behaviors during the light phase and then left undisturbed for at least 3 days before being sacrificed at the middle of the light phase (ZT6) for brain analysis.

2.3. Experiment 2: effects of orexinergic signaling on hypothalamic TH-ir and SST-ir cells

The animals were housed under BLD conditions for four weeks before being treated with daily injections of a selective orexin-1 receptor (OX1R) antagonist SB-334867 (10 mg/kg i.p., Tocris Biosciences, Bristol, UK) or vehicle (60/40 DMSO/saline, 0.4 ml) between ZT 3 and 7 for 5 days. Forced swim test and sweet solution preference test were conducted following the first two daily injections as described in a previous study [7]. Following 5 daily injections of either SB-334867 or vehicle, animals ($n = 6$/group) were sacrificed between ZT 7 and 8.

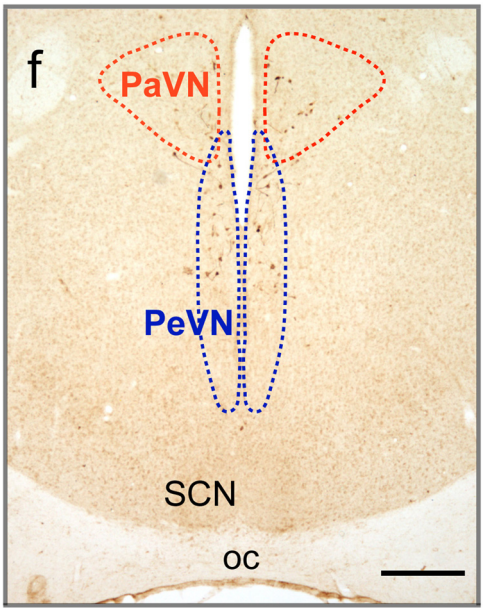

Fig. 1. A representative photomicrograph of TH immunostaining in the hypothalamus of the diurnal grass rat. Dashed lines delineate the hypothalamic PaVN and PeVN regions where the TH and SST cells were counted. Other landmarks labeled on the image are the fornix (f), optic chiasm (oc) and suprachiasmatic nucleus (SCN). Scale bar, 300 μm.

2.4. Immunocytochemistry (ICC)

Following transcardial perfusion, brains were removed and fixed with 4% paraformaldehyde, cryoprotected, and sectioned at 40 μm using a cryostat (Leica, IL). ICC was carried out as in previous studies [1,7] using the primary antibodies TH (1:5000, sc-7847, Santa Cruz) or SST (1:10,000, sc-13099, Santa Cruz). Sections were then processed with the avidin-biotin-immunoperoxidase (ABC) technique using DAB as the chromogen.

2.5. Quantification of TH-ir and SST-ir

Images of the brain sections were obtained using a CCD video camera attached to a light microscope. The hypothalamic paraventricular nuclei (PaVN) and periventricular nuclei (PeVN) where the TH-ir and SST-ir cell bodies were analyzed are shown in Fig. 1. The TH- and SST-ir cells were counted bilaterally by researchers blind to the experimental conditions. The PaVN was analyzed at the level equivalent to panel 41–46, while PeVN was analyzed at the level equivalent to panel 38–46 in the rat brain atlas [27]. There was no significant interaction between region and treatment condition (two-way ANOVA) in both experiment 1 and 2. Therefore, the combined cell counts from the two regions were reported. One-way ANOVAs followed by Tukey post-hoc tests were used to assess the effect of lighting condition (BLD/DLD/SP) on the number of TH-ir and SST-ir cells. Student's *t*-tests (two-tailed) were used to test the effect of the OX1R antagonist. $p < 0.05$ was considered as significant.

3. Results

3.1. The number of hypothalamic TH-ir and SST-ir cells is attenuated following light deficiency

TH-ir cells were found in both PaVN and PeVN of the hypothalamus sub-regions (Fig. 2A), Compared to grass rats in the BLD

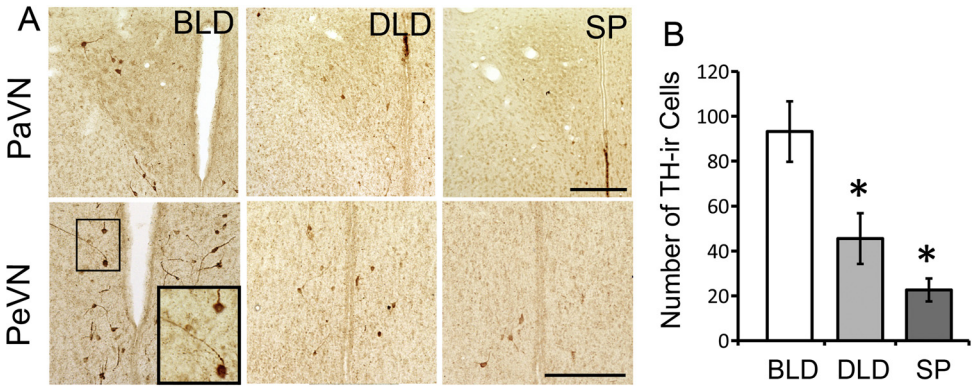

Fig. 2. TH-ir cells are reduced following exposure to winter-like lighting conditions. (A) Representative staining for TH immunoreactivity (ir) in the PaVN and PeVN under the three lighting conditions: BLD (12:12 h bright light:dark), DLD (12:12 h dim light:dark) and SP (8:16 h short photoperiod). Black box indicates two TH-ir cells shown at higher power. (B) Number of TH-ir cells in BLD, DLD and SP conditions. Data are shown as mean ± sem ($n = 6$). * indicates $p < 0.05$. Scale bar, 100 μm.

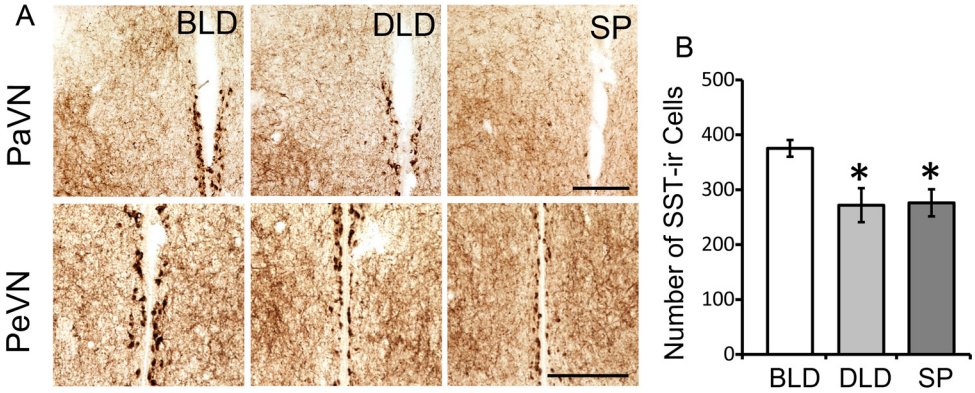

Fig. 3. SST-ir cells are reduced following exposure to winter-like lighting conditions. (A) Representative staining for SST immunoreactivity (ir) under the three lighting conditions: BLD (12:12 h bright light: dark), DLD (12:12 h dim light: dark) and SP (8:16 h short photoperiod). (B) Number of SST-ir cells in BLD, DLD and SP conditions. Data are shown as mean ± sem ($n = 6$). * indicates $p < 0.05$. Scale bar, 100 μm.

group, there were fewer TH-ir cells in the hypothalamus of DLD and SP animals. Quantitative analysis revealed a significant effect of lighting condition on the number of TH-ir cells (one-way ANOVA, $F_{2,14} = 11.74$, $p = 0.001$), with the number in DLD or SP lower than BLD (post-hoc Tukey test, $p < 0.05$, Fig. 2B). SST-ir cells were observed mainly within the PeVN (Fig. 3A). In the PeVN, SST-ir cells are located adjacent to the third ventricle, more medial compared to the distribution of the TH-ir cells. There was also a significant effect of lighting condition on the number of SST-ir cells (one-way ANOVA, $F_{2,14} = 4.93$, $p = 0.024$), with the number in DLD or SP lower than that in BLD (post-hoc Tukey test, $p < 0.05$, Fig. 3B).

3.2. *Blocking orexinergic signaling leads to a reduction in the hypothalamic TH-ir*

Animals housed in the BLD condition were treated with either a selective OX1R antagonist or vehicle. There was a significant reduction of TH-ir cells in the antagonist treated group compared to vehicle treated control group (*t*-test, $t_{10} = 6.05$, $p < 0.001$, Fig. 4A). In contrast, there was no significant difference in the number of SST-ir cells between the antagonist treated and control groups ($t_{10} = 0.64$, $p = 0.53$, Fig. 4B).

4. Discussion

The present study revealed that in diurnal grass rats housed in winter-like lighting conditions, i.e. DLD or SP, there was a significant reduction in the number of TH-ir and SST-ir cells in the PaVN and PeVN of the hypothalamus. Our results on TH-ir cells are consistent with the finding in nocturnal Long Evans rats, which showed that pro-depression lighting conditions lead to a decrease in the number of hypothalamic DA cells [9]. It was proposed therein that changes in the number of TH-ir cells occurred via neurotransmitter switching, whereby SST-ir neurons changed chemical phenotype to express dopamine [9]. However, in contrast to a predicted decrease of TH-ir accompanied with an increase in SST-ir as seen in nocturnal rats, we observed a decrease in both TH- and SST-ir in diurnal grass rats housed under pro-depression lighting conditions (Fig. 4). Furthermore, in diurnal grass rats, the TH- and SST-ir cells show distinct distributions in the hypothalamus with little over-

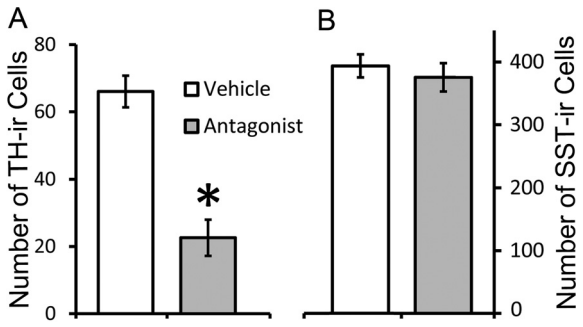

Fig. 4. Treating BLD animals with a selective OX1R Antagonist (SB-334867, 10 mg/kg) significantly reduced the number of hypothalamic TH-ir cells (A), but had no effect on the number of SST-ir cells (B). Data are shown as mean ± sem ($n = 6$). * indicates $p < 0.05$.

lap (Figs. 2 and 3). Thus, a switch between DA and SST chemical phenotypes is unlikely to be the mechanism through which TH-ir is reduced in diurnal grass rats under the pro-depression DLD condition.

Photoperiodic changes in TH-ir and DA metabolism in the hypothalamus have been reported in species showing seasonal breeding patterns and have been implicated in regulating seasonal reproductive functions [12,34]. The grass rats used in our study are from a natural habitat 3°S of the equator that does not undergo seasonal photoperiodic changes [24]. However, in the wild, the grass rats usually show a seasonal breeding pattern with a sexual resting period during the dry season followed by a breeding period during the rainy season [33]. The BLD condition may represent the sunny days during dry season, while the DLD and SP conditions may represent decreased environmental lighting during the rainy season. Thus, changes in their hypothalamic DA system observed under SP or DLD may regulate the reproductive functions during rainy seasons when the ambient light intensity is reduced. On the other hand, the hypothalamic DA neurons may also be involved in modulating the nonreproductive traits, e.g. the behavioral and affective adaptation and/or maladaptation associated with altered ambient lighting conditions [8]. Although entering an energy conserving state during the winter could constitute an adaptive evolutionary mechanism that aided the survival for our ancestors, the recurrent winter depression in SAD is undoubtedly a maladaptation in the modern era [6,10].

The neural mechanisms underpinning SAD are not well understood, with the leading theory focusing on the circadian component, i.e. a misalignment between an individual's circadian rhythms and the environment [20,21]. Although circadian system disturbances are associated with mood disorders [2,14,15], recent work has shown that lighting conditions can also impact mood and anxiety independent from circadian regulation, e.g. through the intrinsic photosensitive retinal ganglion cells [19] or direct retinal-raphe projection [30]. Our previous work revealed that orexin neurons in the hypothalamus are involved in mediating the effects of ambient light on mood and anxiety in the diurnal grass rats [1,7]. In the present study, we found that inhibiting orexinergic transmission using a selective OX1R antagonist, SB-334867 in grass rats housed in BLD conditions led to a significant reduction of hypothalamic TH-ir cells. The number of TH-ir cells in the antagonist-treated group was comparable to those observed in DLD or SP animals. Furthermore, animals in these three comparable pro-depression conditions show increased depression-like behaviors compared to those in BLD group [4,7,17,18]. The results indicate that the hypothalamic DA cells are related to the prevailing affective state. The results also suggest that changes in the number of hypothalamic DA neurons stem from light-dependent changes in the orexinergic system. Orexinergic innervation and OX1R have been found in the hypothalamus including the PaVN and PeVN of grass rats and laboratory rats [5,23,28,35], which is in accordance to a direct orexinergic modulation in these regions. The changes in the environmental lighting conditions may regulate the level of orexin released into the target sites and/or the expression of orexin receptors in brain regions involved in mood regulation. This potential mechanism through which the orexin system mediates the effects of light on emotional behaviors will be investigated in future studies.

In summary, the present study revealed that in diurnal grass rats, hypothalamic DA neurons are influenced by changes in ambient lighting and are associated with the affective state. Moreover, changes in the hypothalamic DA neurons are likely mediated by orexinergic pathways. The orexin system has been implicated in a variety of functions including the regulation of sleep/wake cycle, eating, rewarding pathways and emotions, which are all affected in SAD [13,22,32]. The results from the present study and our previous work [1,7] collectively suggest that the orexinergic pathways play a key role in mediating the effects of ambient lighting conditions on other brain systems linked to mood regulation. Elucidating the neural mechanisms underlying light-dependent changes in mood and anxiety will contribute to the development of more effective strategies for SAD treatment and prevention.

Conflict of interest

There is no conflict of interest concerning the authors in conducting this study and preparing this manuscript.

Contributors

SD and WA conducted the experiment, analyzed the data and wrote the manuscript. LY designed the experiment and wrote the manuscript.

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