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Research report

Antidepressant-like effect of bright light is potentiated by L-serine administration in a mouse model of seasonal affective disorder

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ABSTRACT

Bright light therapy is used as the primary treatment for seasonal affective disorder; however, the mechanisms underlying its antidepressant effect are not fully understood. Previously, we found that C57BL/6J mice exhibit increased depression-like behavior during a short-day condition (SD) and have lowered brain serotonin (5-HT) content. This study analyzed the effect of bright light on depression-like behaviors and the brain serotonergic system using the C57BL/6J mice. In the mice maintained under SD, bright light treatment (1000 lx, daily 1 h exposure) for 1 week reduced immobility time in the forced swimming test and increased intake of saccharin solution in a saccharin intake test. However, the light treatment did not modify 5-HT content and selective 5-HT uptake in the amygdala, or temporal patterns of core body temperature and wheel-running activity throughout a day. In the next experiment, we attempted to enhance the effect of bright light by using L-serine, a precursor of D-serine that acts as an *N*-methyl-D-aspartic acid receptor coagonist. Daily subcutaneous injection of L-serine for 2 weeks prior to the bright light strongly reduced the immobility time in the forced swimming test, suggesting a synergistic effect of light and L-serine. Furthermore, bright light increased the total number of 5-HT-immunoreactive cells and cells that had colocalized 5-HT and c-Fos immunosignals in several subregions of the raphe nuclei. These effects were potentiated by prior injection of L-serine. These data suggest that the bright light may elicit an antidepressant-like effect via enhanced 5-HT signals in the brain and L-serine can enhance these effects.

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1. Introduction

Seasonal changes in photoperiod regulate mammalian physiology and behavior. Seasonal affective disorder (SAD) is a subtype of major depressive or bipolar disorders that follow the seasonal pattern of major depressive episodes occurring at a specific time of the year (Rosenthal et al., 1984). Symptoms of SAD include depression, with the associated diminished pleasure or interest, feelings of worthlessness, and decreased ability to think or concentrate. Most SAD patients also report atypical symptoms including hypersomnia, hyperphagia, decreased energy levels, and carbohydrate craving (Rosenthal et al., 1984). Bright light therapy is used as the primary treatment for SAD (Lewy et al., 1982; Terman et al., 1989; Oldham and Ciraulo, 2014). Although mechanisms underlying SAD remain elusive, numerous studies suggest the involvement of the brain serotonergic system (Carlsson et al., 1980; Lambert et al., 2002; Gupta et al., 2013). Additionally, the circadian phase-shift hypothesis has been proposed based on the observation that the internal circadian rhythms of SAD patients are phase-delayed relative to the external clock or other rhythms, such as sleep-wake cycle (Lewy et al., 1987). In this theory, bright light therapy exerts an antidepressant effect through phase-advance of the clock. However, there is still some controversy regarding the involvement of circadian system (Oldham and Ciraulo, 2014).

There are several proposed animal models of SAD, including diurnal rodents (fat sand rats: Einat et al., 2006 grass rats: Leach et al., 2013) and Siberian hamsters (Prendergast and Nelson, 2005). In grass rats, daytime light deficiency under 12 h light and 12 h darkness (12L12D) increases stress-induced immobility and decreases the number of serotonin (5-HT)-immunoreactive neurons (Leach et al., 2013), suggesting a link between light and the brain serotonergic system. However, mechanistic analysis has

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not been advanced in detail because of a lack of inbred laboratory animal models. This is due to a conventional premise that laboratory mice and rats, being non-seasonal breeders, are inappropriate for the investigation of photoperiod-related functions. Recently, however, we clarified that compared to C57BL/6J mice under long-day condition (LD), those under short-day conditions (SD) exhibit an increased immobility in the forced swimming test (FST), a depression-like behavior, and reduced intake of saccharin, a depression-related anhedonic behavior, with lowered 5-HT content in the amygdala (Otsuka et al., 2014). These mice also showed increased intake of sucrose and high sensitivity of 5-HT synthesis to glucose, which may reflect carbohydrate craving in patients with SAD (Otsuka et al., 2014). From these findings, C57BL/6J mice may serve as a useful tool for elucidating the mechanisms of SAD.

Predictive validity is a crucial criterion that animal models for psychiatric disorders should fulfill. This study first evaluated the antidepressant-like effect of bright light in C57BL/6J mice under SD. We further examined the effect of bright light on the brain serotonergic system and rhythm profiles of wheel-running activity and core body temperature. Because *N*-methyl-D-aspartic acid (NMDA) receptors are suggested to play a pivotal role in light signaling in the brain and 5-HT system (de Kock et al., 2006; Albrecht, 2012), we attempted to enhance the antidepressant-like effect of bright light by administration of L-serine, a precursor of D-serine that acts as an NMDA receptor coagonist. Finally, we examined bright light- and/or L-serine-induced modulation of serotonergic signals in the raphe nuclei by analyzing 5-HT and c-Fos immunoreactivity.

2. Materials and methods

2.1. Animals

Male 4-week-old C57BL/6J mice were obtained from Japan SLC (Shizuoka, Japan). Mice were housed in a group of three or four animals. After acclimation for 1–2 weeks, they were exposed to SD [8 h of light (5 lx), 16 h of darkness] or LD [16 h of light (100 lx), 8 h of darkness] as indicated below. The light intensity under SD sufficiently caused increased depression-like behavior in our previous study (Otsuka et al., 2014). Light was supplied by a white LED light bulb (ELG-01B(W), light ranging from 400 to 700 nm, peak: 440–460 nm, Asahi Electric Corporation, Osaka, Japan). The animal boxes were placed in a room at a temperature of 25 ± 1 °C. Water and a standard diet for laboratory rodents (MF, Oriental Yeast, Tokyo, Japan) were available ad libitum. All animal experiments were conducted in accordance with the Guidelines for Animal Experiments of the Faculty of Agriculture at Kyushu University, as well as the Law (No. 105) and Notification (No. 6) of the Japanese Government. All experiments were approved by Animal Care and Use Committee of Kyushu University under permission number A24-044-0.

2.2. Experiment 1: Effect of bright light on behaviors and brain 5-HT contents and uptake

To clarify the effect of photoperiod and bright light on depression- and anxiety-like behaviors and on the brain serotonergic system, mice were randomly divided into 3 weight-matched groups (n = 12–13) after acclimation. The first and second groups were maintained under SD and LD for 3 weeks, respectively. The third group was maintained under SD for 2 weeks, followed by bright light treatment (LP) under SD for 1 week. Bright light treatment involved daily exposure to 1000 lx light (LDA4N-H-G570, light ranging from 400 to 700 nm, peak: 440–460 nm, Asahi Electric Corporation) under SD at Zeitgeber time (ZT, ZT0 represents light onset) 1–2 with timing controlled by an automatic scheduler module attached to the light bulb. Next, behavioral tests were started. Mice were maintained under SD, LD, and LP conditions until the end of the experiment including behavioral test periods. For behavioral testing, the open field test (OFT, a test for spontaneous activity in a novel environment and anxiety-like behavior) and the FST (test for depression-like behavior) were performed 2 days apart. Tests were performed during light periods, i.e., ZT2.5–4, under white light (5 lx). Four days after the FST, mice were euthanized by decapitation under deep anesthesia with isoflurane gas, and the amygdala samples were dissected at ZT2, 10, and 18 (n = 4–5) for analysis of levels of 5-HT and its major metabolite, 5-hydroxyindoleacetic acid (5-HIAA), by high performance liquid chromatography (HPLC). Euthanasia during the dark phase was performed under dim red light. Analysis was performed using the amygdala samples, because (1) in humans, seasonal variations in 5-HT transporter binding are reported in a corticolimbic circuit comprising the amygdala and medial prefrontal cortex (Praschak-Rieder et al., 2008), (2) bright-light intervention negatively affected threat-related amygdala and prefrontal reactivity in humans (Fisher et al., 2014), and (3) our previous study using mice showed that the photoperiod regulates 5-HT and 5-HIAA levels in the amygdala, but not in other brain regions such as the hypothalamus (Otsuka et al., 2014).

Another batch of animals was maintained under LD, SD, and LP (n = 9–11) in the same way as above, and used for the saccharin intake test (a test for anhedonia/depression-like behavior) during the dark period (ZT22-23). This timing was selected based on a previous study that showed photoperiodic changes in the intake of sweet solutions without changes in food and water intake (Otsuka et al., 2014).

For the 5-HT uptake assay, mice maintained under LD, SD, and LP were decapitated under deep anesthesia with isoflurane gas at ZT2, 6, and 10 (n = 4), and tissue samples of the amygdala (two samples per animal, from left and right hemispheres) were punched out from 0.5-mm-thick brain slices using a needle of 2.2 mm diameter. These timings were selected to determine temporal 5-HT uptake after bright light treatment.

2.3. Experiment 2: Effect of bright light on the rhythms of wheel-running activity and core body temperature

To determine the effect of photoperiod and bright light on the phase relationship between rhythms of wheel-running activity and core body temperature, mice were intraperitoneally implanted with thermo loggers (Thermochron SL, KN Laboratories, Osaka, Japan) under anesthesia with isoflurane, and individually housed in a cage equipped with a running wheel. Temporal patterns of wheel-running activity were measured using a computer system (Chronobiology Kit, Stanford Software Systems, Palo Alto, CA). They were maintained under LD, SD, or LP (n = 8) for 3 weeks, and their rhythm profiles of wheel-running activity and core body temperature were analyzed during the last 7 days. ClockLab software (Actimetrics, Evanston, IL) was used to determine the rhythm profiles. Dark onset in each lighting condition was aligned to compare the rhythm profiles between lighting conditions.

2.4. Experiment 3: Effect of bright light and L-serine on behaviors and 5-HT neurons

This experiment was conducted to analyze the synergistic effect of bright light and L-serine administration. After acclimation under SD for 3 weeks, mice were randomly divided into 4 weight-matched groups (n = 8–10). The first and second groups were maintained under SD with a daily subcutaneous (s.c.) injection of saline (vehicle) or L-serine (5 mmol/kg), respectively, 15 min prior to ZT1. The third and fourth groups were exposed to LP (1000 lx light at ZT1-2 under SD) with a daily s.c. injection of saline or L-serine,

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