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The Effects of Blue LED Light on Behavior and Retinal Function in Maternal and Offspring Mice

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Abstract

In the present study, we investigated whether blue light emission diode (LED) light exposure affects the maternal behavior of mice. The brain function of the offspring mice, including short-term memory, locomotor activity, anxiety-like behavior, and depression-like behavior, was evaluated. Pregnant mice at day 11 were housed in the apparatus for exposure to blue LED light during the daytime. Nesting behavior and the survival of pups were observed until weaning. After weaning, the offspring mice were bred in normal light conditions until 12 weeks old, and then the Y-maze test, open field test, and tail suspension test were performed. Retinal functions were evaluated by electroretinogram and histological analysis. Blue LED light exposure during the daytime induced retinal damage, but did not affect behavior related to maternal care in maternal mice. In the offspring mice, blue LED light exposure during the daytime did not affect the retina or brain functions. These findings suggest that blue LED light during the daytime might not be a risk factor for disruption of the mother-infant relationship or offspring brain development in mice.

Keywords

Blue LED Light, Maternal Behavior, Daytime, Retina, Brain

1. Introduction

Recently, exposure to light emission diode (LED) light has increased due to the emergence of digital devises containing video displays such as personal comput-

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ers, smart phones, and the other devices that use illumination. Video displays emit a large amount of blue light (400 - 500 nm), and blue light has been reported to be harmful to the retina [1] [2]. Previously, we reported the harmful effects of blue LED light to the retina *in vitro* and *in vivo* [2] [3]. On the other hand, blue LED light has been reported to regulate the circadian rhythm [4] [5], and glucose metabolism [6]. However, an unknown physiological effect of blue LED light for higher brain function may be still present and needs to be clarified.

White LED light may be spreading to companies supplying experimental animals and biomedical research institutions to reduce the consumption of electricity in the near future. Thus, it is critical to elucidate the effects of LED light on breeding behavior and physiology in housed animals. However, there are few studies to date evaluating the effects of LED light.

Maternal behavior is common to mammals, and includes nursing, nest building, maternal aggression, licking, grooming, retrieving and other behaviors [7] [8]. Since the mother-infant relationship is indispensable for species continuation, the basic brain mechanisms that control maternal behavior are considered to be well conserved in evolution [9]. Previous reports showed that disruption of the mother-infant relationship induced cognitive and emotional dysfunction [10]. It is an important finding that environmental factors can affect maternal behavior to research for mental diseases which derive from stressors in the developmental stage of brain.

In the present study, we investigated whether blue LED light exposure affects the maternal behavior of mice. Furthermore, the brain function of the offspring mice, including short-term memory, locomotor activity, anxiety-like behavior, and depression-like behavior, was evaluated.

2. Materials and Methods

2.1. Animals

Pregnant ICR mice were purchased from Japan SLC (Shizuoka, Japan) at day 10 of pregnancy. Pregnant females and pups were housed individually in specific pathogen-free conditions with ALPHA-dri (Shepherd Specialty Papers, USA) bedding. Animals were housed at 24˚C ± 2˚C under a 12-hr light cycle (8:00 to 20:00) and had access to food and water ad libitum. In this experiment, 10 dams were used and total 136 pups were produced. Then, total 26 male offsprings were used for behavioral tests for brain functions. All procedures relating to animal care and treatment conformed to the animal care guidelines issued by the Gifu Pharmaceutical University Animal Experiment Committee. The protocol for this study was approved by the Committee on the Ethics of Animal Experiments of the Gifu Pharmaceutical University.

2.2. Exposure to Blue LED Light at Subjective Daytime

Female mice at day 11 of pregnancy were exposed to 100 lux of blue LED light (12 hr per day, 4 weeks, lights on 8:00) (World Trading Co., Ltd, Kanagawa, Japan). To mimic the light from a display of smart phones (measured at 10 cm

distance), the intensity (100 lux) was chosen. The ambient temperature during exposure to blue LED light was maintained at 24˚C ± 2˚C. Control mice were housed in conditions with 20 to 50 lux of fluorescent light.

2.3. Measure of Maternal Behavior

2.3.1. Nesting Behavior

As one of assessment of maternal behavior, nest building was measured as previously described [11] [12]. Nests were observed daily from the outside of cages. The quality of the nest was determined using following scale; score 0, a nest was not built or unidentified; score 1, a flat nest can be identified; score 2, a nest that looks like a soup plate; score 3, a hemisphere-like nest with a consecutive bank.

2.3.2. Survival Rates of Pups

The number and the average body weights of newborn pups were measured daily. To minimize environmental changes, the body weights of maternal mice and their pups were measured no earlier than 3 days after delivery. Throughout the experiment, mice were monitored for any sign of injury or weakness.

2.4. Behavioral Tests in Male Offspring Mice from Blue LED Light-Exposed Dams

After the experiment for maternal behavior, the pups brought up by maternal mice that had been exposed to blue LED light for 4 weeks were grown in normal light conditions until 12 weeks old. To assess the effects of exposure to blue LED light during childhood on the brain development, offspring mice were exposed to blue LED light together with their dams during the childhood period (postnatal day 0 to 21), then were brought up at 12 weeks old in normal light conditions.

2.4.1. Open Field Test

The open field test was performed to assess locomotor activity and anxiety-like behavior, as previously described [13]. Mice were placed in an open field apparatus (length 30 cm × width 30 cm × height 30 cm) that was made of wood. The mouse was allowed to explore the apparatus for 60 min. In this test, the behavior of the mouse was recorded. Before starting a new trial, the apparatus was cleaned with 70% ethanol and dried using paper towels and a fan to minimize the influence of odor. The total distance moved was measured from the video file using a computer-operated EthoVision XT system (Noldus, Wageningen, Netherlands). The time spent in the central zone (length 15 cm × width 15 cm × height 15 cm) was used as a marker of anxiety-like behavior.

2.4.2. Y-Maze Test

The Y-maze test was performed to assess short-term memory, as previously described [14]. The Y-maze was made of three gray plastic arms (length 40 cm × width 10 cm × height 12 cm). After habituation for an hour, each mouse was placed in the end of an arm and allowed to freely explore the maze for 8 min.

During the test, behavior was recorded. The number and order of the arms entered were counted from the video file. Entering each of three arms in turn was defined as an alternation. Alternation was calculated by the following formula:

$$\text{Alternation}\ (\%) = \left[\text{the number of actual alternations}/\text{the total number of entering each arm} - 2\right] \times 100$$

2.4.3. Tail Suspension Test

The tail suspension test was performed to assess depression-like behavior, as previously described [15]. Each mouse was suspended by the tail with a 50 cm strip of surgical tape above the floor, and their behavior was recorded for 8 min. Immobility time was measured automatically using a computer-operated EthoVision XT system. Mice were determined to be immobile when the mobility score of the system was less than 10%.

2.5. Electroretinogram

Electroretinogram (ERG) was recorded 7 days after blue LED light exposure in maternal mice and 12 weeks after blue LED light exposure to dams in male offspring. The mice were housed in a completely dark room for 24 hr (dark adaptation), after which they were anesthetized using ketamine (120 mg/kg, i.p.; Daiichi-Sankyo, Tokyo, Japan) and xylazine (6 mg/kg, i.p.; Bayer Health Care, Tokyo, Japan). The pupils were dilated with 2.5% phenylephrine and 1% tropicamide (Santen Pharmaceuticals, Osaka, Japan). In the left eyes of dark-adapted mice, flash ERG was recorded by placing a gold ring electrode (Mayo, Aichi, Japan) in contact with the cornea and a reference electrode (Nihon Kohden, Tokyo, Japan) on the tongue. A neutral electrode (Nihon Kohden) was inserted subcutaneously near the tail. High pass filtering (0.3 Hz) and low pass filtering (500 Hz) were used. All procedures were performed under red twilight, and mice were kept on heating pads (Mycoal, Tochigi, Japan) to maintain a steady body temperature during ERG recordings. The amplitude of the (a) wave was measured from the baseline to the maximum (a) wave peak, and the (b) wave was measured from the maximum (a) wave peak to the maximum (b) wave peak.

2.6. Histological Analysis

After ERG recording, the mice were euthanized by decapitation. Each eye was enucleated and kept immersed for 24 hr at 4˚C in a fixative solution containing 4% paraformaldehyde. Three paraffin-embedded sections (thickness 5 μm) were cut from the optic disc, which were prepared in the standard manner. Retinal sections were stained with hematoxylin and eosin. Retinal images were photographed by light microscopy (BZ-X710; Keyence, Osaka, Japan), and the thickness of the outer nuclear layer (ONL) from the optic disc was measured at 240 μm intervals. Data from these sections were averaged for each eye.

2.7. Statistical Analyses

All data are expressed as the mean ± standard error of the mean (SEM). Statis-

tical comparison was made using Student's t-tests or Mann-Whitney U tests (Figure 1(A)). A value of $p < 0.05$ was considered to be significant.

3. Results

3.1. Blue LED Light Exposure Did Not Affect Maternal Behavior

To investigate the effects of blue LED light exposure during the daytime on maternal care in maternal mice, we observed their nesting behavior, the number of pups, and the body weight of pups.

We evaluated nesting behavior as a measure of maternal care related behaviors. All of the maternal mice built nests, and the scores of nests did not differ between each group ($p = 0.85$, n = 5, Figure 1(A)). The number of pups from blue LED light-exposed mice did not differ from control mice (postnatal day 23; $p = 0.14$, n = 5, Figure 1(B)). Moreover, the survival rate or the development of pups did not differ between each group (postnatal day 23; $p = 0.62$, n = 5, Figure 1(C)).

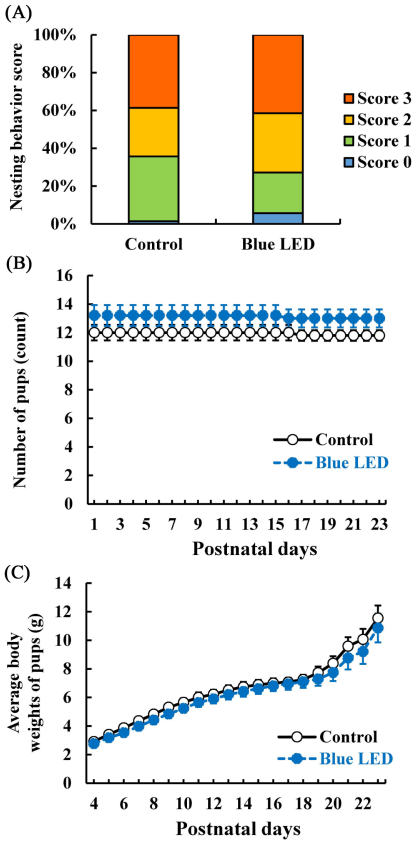

Figure 1. Evaluation of maternal behaviors by exposure to blue LED light in maternal mice. (A) Nesting behavior was measured on postnatal day 1 to 14. The quality of the nest was determined using the following scale; score 0, a nest was not built or unidentified; score 1, a flat nest can be identified; score 2, the nest looks like a soup plate; score 3, a hemisphere-like nest with a consecutive bank. (n = 5); (B) The number of surviving pups was counted on postnatal day 1 to 23; (C) The body weight of pups was measured on postnatal day 4 to 23. Each column represents the mean ± S.E.M. (n = 5).

3.2. Blue LED Light Exposure Decreased Visual Function in Maternal Mice

To clarify whether exposure to blue LED light during the daytime (100 lux for 4 weeks) induces retinal damage in maternal mice, both electrophysiological and histological analysis were performed. Firstly, the effects of blue LED light exposure on visual function in maternal mice were evaluated by electrophysiological analysis. Representative amplitudes of recorded ERG are shown in Figure 2(A). The (a) wave amplitudes indicate the photoreceptor function, and the (b) wave amplitudes reflect the function of bipolar and Müller cells. Therefore, decreases in (a) and (b) wave amplitudes indicate retinal dysfunction (flash intensity 0.98 log cd/m^2; (a) wave; $p = 0.001$, (b) wave; $p = 0.012$, n = 5, Figure 2(B) and Figure 2(C)).

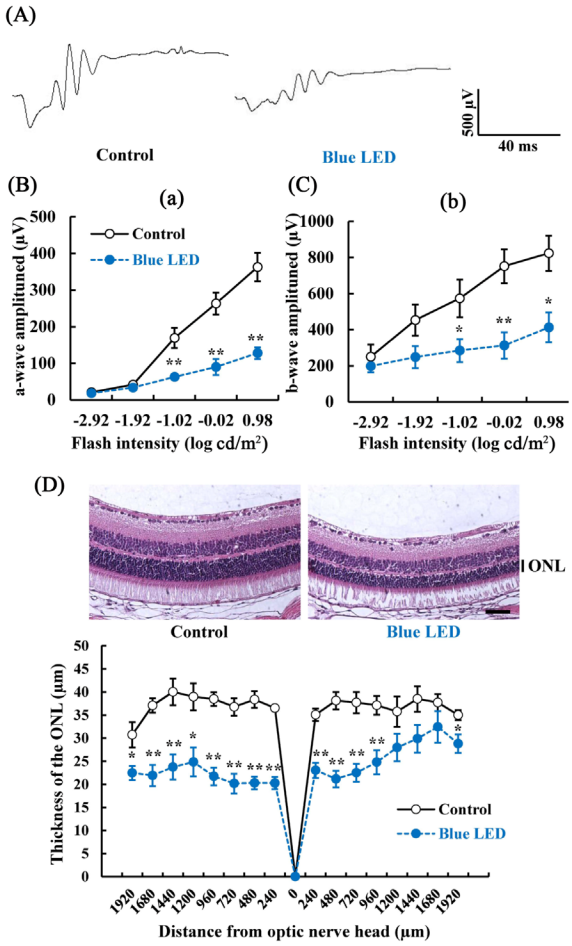

Figure 2. Measurement of retinal function after exposure to blue LED light in maternal mice. (A) Typical traces of dark-adapted ERG responses were measured 7 days after exposure to blue LED light. Stimulus flashes were used from 0.98 log cds/m^2; ((B), (C)) Amplitudes of (a) and (b) waves of blue LED light exposure (100 lux for 4 weeks); (D) Measurement of the thickness of the outer nuclear layer 7 days after blue LED light exposure. Upper images are representative images of retinal sections. Each column represents the mean ± S.E.M. (n = 5). *; $p < 0.05$, **; $p < 0.01$ vs. control group (Student's *t*-test). The horizontal scale bar represents 50 mm.

Next, the effects of blue LED light exposure on visual function in maternal mice were also evaluated by histological analysis. Representative retinal images from optic nerves of maternal mice were taken 7 days after blue LED light exposure finished (Figure 2(D)). The outer nuclear layer (ONL) in the blue LED light-exposed mice was significantly thinner compared with that in the non-exposed control mice (distances 960 μm; $p = 0.0001$, n = 5, Figure 2(D)). The thickness of the ONL was measured at 240 μm intervals (Figure 2(D)).

3.3. Offspring Mice from Blue LED-Exposed Dams Did Not Show Any Behavioral Changes

Offspring mice were exposed to blue LED light together with their dams during the child-hood period (postnatal day 0 to 21). Male offspring mice were brought up at 12 weeks old in normal light conditions with their littermates. There was no difference in the aver-age body weights of male offspring between each group in 12 weeks old (data not shown). To clarify the effects of blue LED light during the childhood period, behavioral tests were performed. For behavioral tests, total 26 mice (2 or 3 mice per cage) were used.

In the open field test, locomotor activity and anxiety-like behavior were evaluated. Distance moved and duration in the center zone of blue LED light-exposed offspring mice did not differ from non-exposed control offspring mice in the open field test (distance moved at 1 min; $p = 0.08$, duration in the center zone at 1 min; $p = 0.31$, n = 11, Figure 3(C) and Figure 3(D)). The Y-maze test was performed to evaluate short-term memory. The alternation rate and total number of arm entries in blue LED light-exposed offspring mice did not differ from that of non-exposed control offspring mice (alternation rate; $p = 0.25$, total number of arm entries; 0.35, Control; n = 12, Blue LED; n = 13, Figure 3(A) and Figure 3(B)). The tail suspension test was performed to evaluate depression-like behavior. In a tail suspension test, the immobility time did not change between each group (8 min; $p = 0.44$, n = 11, Figure 3(E)), suggesting that blue LED light-exposed offspring did not show depression-like behavior.

3.4. Blue LED Light Did Not Affect Visual Function in Offspring Mice Exposed to Blue LED Light during the Childhood Period

To assess the effects of blue LED light exposure during the childhood period in offspring mice, retinal functions were evaluated. In male offspring mice, ERG amplitudes (representative amplitudes in Figure 4(A); flash intensity 0.98 log cd/m^2; (a) wave; p = 0.26, (b) wave; $p = 0.54$, n = 6, Figure 4(B) and Figure 4(C)) and ONL thickness did not differ between LED light-exposed and control mice (distances 960 μm; $p = 0.11$, Control; n = 5, Blue LED; n = 4, Figure 4(D)).

4. Discussion

In the present study, we hypothesized that blue LED light has harmful effects on maternal mice. However, there was no difference in the nesting behavior or survival rate of pups after exposure to blue LED light, although blue LED light did

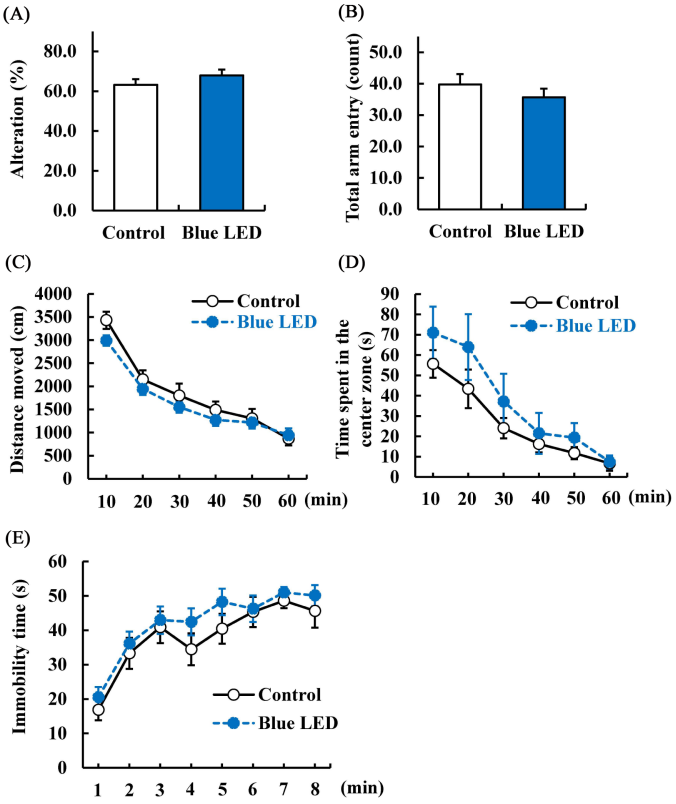

Figure 3. Behavioral analyses of offspring mice after exposure to blue LED light. ((A), (B)) The results of the Y-maze test. (A) The percentage of alternation; (B) Total arm entries in the test. Each column represents the mean ± S.E.M. Control (n = 12), Blue LED light (n = 13); ((C), (D)) The results of the open field test; (C) Total distance moved in 15 min in the novel environment; (D) Duration in the center zone (15 × 15 cm); (E) Immobility time in the tail suspension test. Each column represents the mean ± S.E.M. (n = 11).

induce retinal damage. These findings suggest that blue LED light does not affect maternal behavior, at least in these experimental conditions.

In previous reports, environmental and genetic factors were known to affect the maternal behavior or survival rate of pups [16] [17]. In housing conditions with 60% food restriction or in a cold temperature cage, the rate of female weaning or pups surviving significantly decreased in mice [16]. These reports suggest that severe physical and mental conditions disrupt the mother-infant relationship. In the present study, blue LED light exposure might not severely stress dams or pups or affect brain function.

In the present study, although the retinal function was damaged in blue LED light-exposed dams, there was no difference in the behavior of offspring mice. The reason why visual dysfunction in dams did not affect the behavior of offspring mice remains unclear. In a previous report, maternal behavior was impaired in female mice lacking type 3 adenylyl cyclase, which is required for olfactory signal transduction in the main olfactory epithelium [17]. Moreover, maternal behavior was also impaired in the mice after removal of the olfactory

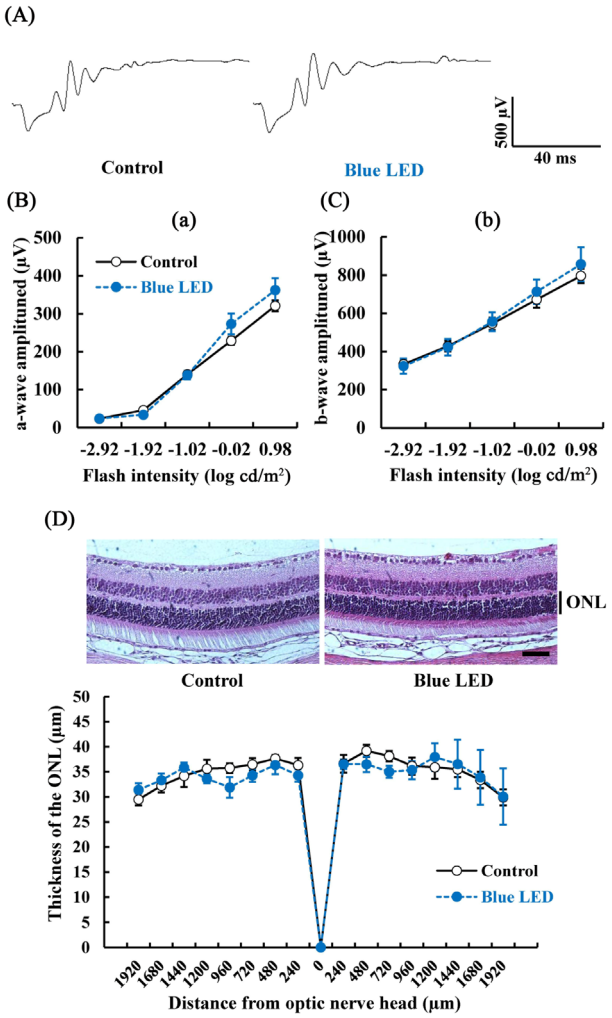

Figure 4. Measurement of retinal function after exposure to blue LED light in offspring mice. (A) Typical traces of dark-adapted ERG responses measured 9 weeks after exposure to blue LED light. Stimulus flashes were used from 0.98 log cds/m^2; ((B), (C)) Amplitudes of (a) and (b) waves of blue LED light exposure (100 lux for 4 weeks); (D) Measurement of the thickness of the outer nuclear layer at 7 days after blue LED light exposure. Upper images are representative images of retinal sections. ONL: outer nuclear layer. Each column represents the mean ± S.E.M. (n = 4 or 5). The horizontal scale bar represents 50 mm.

bulb [18]. Whereas, postpartum female mice showed retrieving behavior after chemosensory cues from pups without the use of audiovisual cues [19] [20]. These reports suggest that olfaction is the most important sense for maternal behavior. The lack of effects on offspring mice in the present study might be due to visual function not significantly contributing to maternal behavior. However, further analyses will be needed to clarify the effects of blue LED light on maternal or offspring mice.

Blue LED light was reported to regulate the circadian rhythm [4] [5]. In previous reports, exposure to light at nighttime, irrespective of the light-dark cycle, was shown to disturb brain functions by disturbing the circadian rhythm [21]

[22]. Disturbance of the circadian rhythm is a risk factor for type 2 diabetes, bipolar disease, and synaptic plasticity dysfunction in the hippocampus [23] [24] [25]. In a previous study, excessive non-normative stimulation with LED light and noises at nighttime on postnatal day 10 - 42 caused cognitive impairment and hyperactivity in mice [26]. In this report, stimulation with light at nighttime for 6 hr was thought to disrupt the circadian rhythm. However, our previous study demonstrated that exposure to blue LED light for a month did not affect memory function, anxiety, or depression-like behavior in C57BL/6J mice [27]. Since disruption of circadian rhythm leads to various physiological changes, in the present study, exposure to light was performed during the light cycle to avoid secondary effects from disruption of the circadian rhythm. A lack of negative effects in offspring mice indicated that exposure to blue LED light during the daytime might not be a risk factor for dysfunction of brain development in offspring mice. The most major difference between a previous report [26] and the present study was the time at which mice were exposed to light. Therefore, the difference of the time of light exposure might lead to the differences in the effects on brain functions. Light exposure that abides to the light-dark cycle might not be harmful to brain functions. However, further studies are needed to clarify a tolerance condition and a time period during which LED light can be used safely during the pregnancy and lactation periods.

5. Conclusion

Blue LED light exposure during the daytime affects visual function, but not behaviors related to maternal care in maternal mice. Nevertheless, blue LED light exposure during the daytime did not affect the retina or brain development in offspring mice. Blue LED light during the daytime might not be a risk factor for disruption of the mother-infant relationship or offspring brain development in mice.

Conflict of Interest

The authors declare that there is no conflict of interest.

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