The Role of Melatonin on Cortisol Level and Anxiety-like Behaviour Induced by Light at Night in Sprague Dawley Rats

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Abstracts

Circadian rhythm disruption due to artificial light at night (LAN) is increasingly recognized as a factor for neuroendocrine and behavioral disturbance. This study investigated the effects of varying nocturnal light intensities on plasma cortisol levels and anxiety-like behavior in male Sprague Dawley rats and evaluated the potential neuroprotective role of melatonin. Twenty-five rats were divided into five groups: Control (dark, 0 lux), Dim light, Dim light with melatonin (DLAN + Mel), Continuous Light Exposure (CLE), and CLE with melatonin (CLE + Mel). Melatonin was administration orally at 10 mg/kg body weight daily for five weeks. Cortisol levels were measured using ELISA, and anxiety-like behavior was assessed via the Open Field Test (OFT). Exposure to dim and continuous light at night elevated plasma cortisol concentrations compared to the control, with the CLE group showing the highest levels. Melatonin administration significantly reduced cortisol levels in the CLE + Mel group ($p < 0.05$) relative to CLE alone. Behavioral analysis showed that light-exposed rats exhibited increased anxiety-like behaviors, indicated by reduced center entries and center time. Melatonin treatment improved exploratory behavior and decreased anxiety-like responses. These findings suggest that higher-intensity nocturnal light exposure exacerbates stress hormone secretion and anxiety, while melatonin mitigates these adverse effects by modulating HPA axis activity and stabilizing circadian rhythm.

***Keywords*:** *melatonin, light at night, cortisol, anxiety-like behavior, circadian rhythm.*

Abstrak

Peran Melatonin terhadap Kadar Kortisol dan Perilaku Mirip Kecemasan yang Dipicu oleh Paparan Cahaya di Malam Hari pada Tikus Sprague Dawley. Gangguan ritme sirkadian akibat paparan cahaya di malam hari semakin diakui sebagai faktor risiko untuk gangguan neuroendokrin dan perilaku. Studi ini menyelidiki efek intensitas cahaya malam yang bervariasi terhadap kadar kortisol plasma dan perilaku yang mirip dengan kecemasan pada tikus jantan Sprague Dawley, serta mengevaluasi peran melatonin sebagai pelindung neuron yang potensial. Sebanyak 25 ekor tikus dibagi menjadi lima kelompok: kontrol, cahaya redup, cahaya redup dengan melatonin (Dim light + Mel), paparan cahaya yang teruss menerus (CLE), CLE dengan melatonin (CLE + Mel). Melatonin diberikan secara oral dengan dosis 10 mg/kg berat badan setiap hari selama 5 minggu. Kadar kortisol diukur dengan metode ELISA, dan perilaku tikus dievaluasi dengan Uji Lapangan Terbuka (OFT). Paparan cahaya redup dan terus menerus di malm hari meningkatkan kadar kortisol plasma dibandingkan dengan kelompok kontrol, dengan kelompok CLE menunjukkan kadar tertinggi. Pemberian melatonin secara signifikan mengurangi level kortisol pada kelompok CLE + Mel dibandingkan dengan kelompok CLE yang tidak diberi melatonin ($p < 0,05$). Analisis perilaku meunjukkan

bahwa tikus yang terpapar cahaya mengalami peningkatan perilaku mirip kecemasan ditandai dengan penurunan frekuensi tikus memasuki area tengah dan lamanya tikus berada di area tengah. Melatonin meningkatkan perilaku eksplorasi dan mengurangi respon yang mirip klecemasan. Temuan ini menunjukkan bahwa paparan cahaya di malam hari meningkatkan sekresi hormon stres dan kecemasan, sementara melatonin mampu meredakan efek buruk yang ditimbulkan tersebut dengan memodulasi sumbu HPA dan menstabilkan ritme sirkadian.

Kata Kunci: *melatonin, cahaya di malam hari, kortisol, perilaku mirip kecemasan, ritme sirkadian)*

Introduction

Circadian rhythms are essential biological processes that regulate a broad spectrum of physiological functions, including metabolism, immunity, and behavior.[1] The synchronization of biological rhythms with the environmental light-dark cycle is a fundamental aspect of mammalian physiology, primarily regulated by the circadian system and its central clock in the suprachiasmatic nucleus (SCN). Nowadays, the rapid development of socioeconomic system and technological progress has led many sectors to operate continuously for 24 hours. Consequently, shift work scheduled have become increasingly common in industry, transportation, and healthcare services. According to reports from European and American labor surveys, approximately 20–26% of the workforce is engaged in shift or night work.[2] Environmental exposure to artificial light at night (ALAN), increasingly prevalent in research and urban settings, is known to induce misalignment of circadian rhythms. This disruption profoundly impacts endocrine function, notably augmenting corticosterone (the rodent equivalent of cortisol) levels and promoting anxiety-like behaviors in animal models.[3] Recent studies demonstrate that such circadian misalignment, induced by constant light exposure or phase shifts, elevates basal and stress-induced corticosterone, disrupts sleep, and increases behavioral indices of anxiety—effects with significant implications for neuroendocrine health and vulnerability to psychiatric disorders.[4]

Chronic exposure to artificial light at night results in higher baseline cortisol levels, altered daily patterns of glucocorticoid release, and can contribute to circadian desynchronization of hormone profiles.[5] Disrupted circadian rhythms in the SCN (through genetic or environmental means) directly cause behavioral despair, helplessness, and increased indicators of anxiety in mouse models.[6] Night workers are often exposed to varying intensities of light during their night shifts or while at home, which may lead to differing physiological and behavioral consequences. However, it remains unclear whether differences in nighttime light intensity produce distinct effects on circadian regulation and related health outcomes.

Based on current condition, we aimed to explores the effects of light at night on melatonin signaling, cortisol regulation, and anxiety-like behavior in Sprague Dawley rats. We wanted to investigate whether varying levels of nocturnal light intensity exert differential impacts on behavioral parameters. Understanding these effects is essential for identifying the extent to which light intensity contributes to circadian disruption among night workers and for developing evidence-based lighting recommendations that can minimize adverse physiological consequences while maintaining alertness and performance during nocturnal work.

Another critical output of this study is melatonin, a pineal gland-derived hormone predominantly secreted at night, which orchestrates physiological processes including sleep, metabolism, and the neuroendocrine response to stress.[4] In nocturnal rodents such as Sprague Dawley rats, the temporal pattern of melatonin release is tightly coupled to the light-dark cycle, and alterations in lighting can disrupt circadian rhythmicity.[7] Therefore, we also aimed to examine melatonin potency in mitigating hypercortisolemia and anxiety-like behavior. Understanding the mechanistic role of melatonin in regulating cortisol and anxious behaviors following circadian

Experimental Section

Chemical and reagents

Melatonin powder (SIGMA Aldrich M5250), Ethanol, NaCl 0,9 %, *Ketamin-Xylazine* (KET-A-XYL®), *PBS* 0,01 M pH=7,4 (SolarBio P1020), Rat Cortisol ELISA Kit (*Finetest* ER1651).

Animals and melatonin preparation

Adult male Sprague-Dawley rats (8-10 weeks old, weighing 200-250 g) obtained from Indonesian Food and Drug Authority were used in this study. This study was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia, with the number KET-278/UN2.F1/ETIK/PPM.00.02/2024. The rats were randomly divided into 5 gropus: Control group (C), group exposed to dim light at night (DLAN), group exposed to DLAN with melatonin (DLAN + Mel), group exposed to Continuous Light Exposure (CLE), group exposed to CLE with melatonin (CLE + Mel). Five rats were used in each group of the study.

Melatonin was first dissolved in a small amount of ethanol, then dissolved in aquadest until it reaches a final ethanol concentration of 1%. The procedure of melatonin preparation was carried out by avoiding exposure to light. The solution was stored in dark bottle.

Experimental protocols

Rats were randomly divided into 5 groups: control group (K), group with circadian rhythm disturbance in the form of dim light at night (DLAN), DLAN + melatonin group (DLAN + Mel), group with circadian rhythm disturbance in the form of Continuous Light Exposure (CLE), CLE + melatonin group (CLE + Mel). In the dark period, the control group received 0 lux exposure, the DLAN group received 5 lux exposure, and the CLE group received 200 lux exposure. Melatonin treatment was given to the DLAN + Mel and CLE + Mel groups through oral administration with a dose of melatonin 10 mg/kg body weight of rats every day at 5:30 pm for five weeks.[8] Before treatment, rats were acclimatized for 1 week. Cortisol hormone levels were examined from plasma samples after all groups of rats received treatment for 5 weeks. The hormone levels in plasma were examined by ELISA.[4]

Three rats were placed in one cage measuring 54 cm x 41 cm x 33 cm in a temperature-controlled room with free access to food and water (ad libitum). The lights were turned off at 6:00 a.m. and turned on at 6:00 p.m. All rats were placed to acclimatitation cage for a week before the experiment started. Light was emitted by dimmable LED strip/downlight lamps placed on the upper wall on shelf facing the cages. The dimmer switch is used to control the intensity of light provided inside the cage. Light intensity was measured with a luxmeter. During the dark period, the control group was exposed to 0 lux (darkness), the DLAN group was exposed to 5 lux (dim light), and the CLE group was exposed to 200 lux (bright light).

Blood sampling

Blood sampling from rats was performed using the retroorbital-plexus method, collecting 2-3 mL (1% of the rat's body weight). Blood plasma samples were used for ELISA testing of melatonin hormones. Before blood collection, the rat were anesthetized with a combination of 0.1 mL of ketamine and 0.05 mL of xylazine. Blood samples were taken from the rat in the morning using a hematocrit and stored in EDTA tubes. The samples were then centrifuged (4°C, 15 minutes, 1000 g). Plasma separation was performed after 30 minutes of standing in EDTA tubes. The plasma fraction was collected and tested immediately or aliquoted and stored at -80°C freezer.

Measurement of cortisol plasma

Frozen plasma samples that have been separated were used for hormone level testing. Reagents from the test kit and the plasma were first left at room temperature before use. Thawed samples are stored in an icebox to prevent sample damage. Cortisol hormone measurements used the Rat Corticosteroid ELISA testing kit (Rat COR ELISA Kit, 96T *Finetest* ER1651) (*Finetest*), with steps adjusted to the kit procedures.[9] Sample

absorbance were read using Thermo Scientific™ Varioskan™ LUX Multimode Microplate Reader at a wavelength of 450 nm. Hormone levels were determined by interpolating sample absorbance values against the melatonin standard curve.

Open Field Test Protocol

Anxiety-like behavior in rats was assessed using the Open Field Test (OFT). Behavioral parameters included the time spent in the central area (center time), frequency of entries into the center area (center entries), and the number of line crossings through the center zone. The test was conducted prior to animal termination. A video camera was positioned above the OFT apparatus and connected to a computer via Bluetooth for data collection. To minimize stress, rats were acclimated to the testing environment for one hour before the behavioral assessment. At the onset of the test, each rat was placed in the center of the arena, and the operator exited the room to maintain a calm environment. The animals were allowed to freely explore the arena for 15 minutes while their behavior was recorded. Upon completion, the video recording was terminated and saved. The arena was thoroughly cleaned with 70% ethanol and wiped dry before testing the next animal. Rats that entered the center zone more frequently were interpreted as exhibiting lower levels of anxiety-like behavior.[9] [10] Video recordings were analyzed using ANY-maze behavioral tracking software.

Statistical Analysis

All data collected were analyzed using GraphPad Prism 10 (GraphPad Software Inc.). Descriptive Statistics were presented as mean ± SEM. Bivariate analysis was performed using analysis of variance followed by Fisher's LSD test. Statistical significance was determined at a *p*-value threshold below 0.05.

Results and Discussion

The effect of melatonin on plasma cortisol level of rat induced light at night

Table 1 shows plasma cortisol of rat induced light at night from control and treatment group. Exposure to low-intensity (5 lux) and high-intensity (200 lux) light during the nocturnal phase induced alterations in the plasma cortisol profile of rats. The cortisol data conformed to assumptions of normality (Shapiro–Wilk test, $p > 0.05$) and homogeneity of variance (Brown–Forsythe test, $p > 0.05$).

Based upon the normality and homogeneity test, ANOVA followed by Fisher's LSD test were performed. Disruption of the circadian rhythm resulting from nocturnal light exposure led to an elevation in plasma cortisol concentrations in both dim-light and continuous-light-exposure groups relative to the control, eventhough there is no significancy between the group (p=0.63; p=0.06; in sequence). Meanwhile, as illustrated in figure 1, a significant difference was observed in plasma cortisol levels between the CLE + Mel group and the CLE group (p=0.024), indicating that melatonin administration markedly reduced plasma cortisol concentrations compared to the group without melatonin treatment. These findings showed that exogenous melatonin effectively mitigates the hypercortisolemic response associated with light-induced circadian disruption.

In this study, we investigated whether circadian disruption using light at night alters plasma cortisol of the rat. We found that exposure to light at night for 5 weeks increased cortisol levels in plasma in both rats exposed to dim light and those exposed to bright light compared to the control group. This is consistent with several studies that conducted experiments with both chronic and acute exposure to light. Exposure of rats and other nocturnal rodents to light during their dark phase (subjective night) or chronically elevated light conditions consistently causes an acute or sustained increase in plasma glucocorticoid or cortisol levels.[11]

Post-hoc comparisons showed a significant increase in cortisol at Circadian Time following 1 hour of light exposure in rats, suggesting that light exposure occurring at an unexpected time results in a stress response.[11] Meanwhile, on another chronic exposure of current study, in one study using male rats, exposure to high intensity artificial light at night (LAN) led to significant cortisol changes. Specifically, cortisol levels in groups exposed to light intensities of 5000 lux and 8000 lux increased significantly compared to the control group after 7 days of exposure.[12]

Table 1. Plasma cortisol level of control and treatment group, obtained from any-maze software

Group	Plasma ortisol level (ng/mg) (mean ± SEM)
Control	14.82 ± 1.665
Dimlight	17.40 ± 2.60
Dimlight + Mel	15.99 ± 0.88
CLE	19.74 ± 1.61
CLE + Mel	13.80 ± 1.42

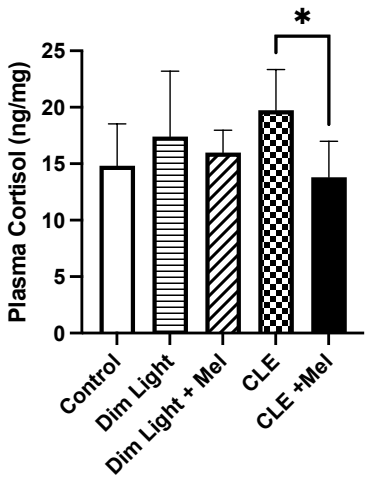

Figure 1. Comparison of cortisol plasma level in the Control Group, Dim light, Dim light + Mel, CLE, and CLE + Mel. Data were shown as mean ± SD and tested according to ANOVA followed by the Fisher's LSD Test between groups. * Significant difference ($p < 0.05$). Dim light: Group exposed to dim light (5 lux) at night, CLE: Continuous Light Exposure, Group exposed to bright light (200 lux) at night. One Way Anova test, followed by LSD: * significant difference ($p \leq 0.05$).

The group given melatonin showed a decrease in cortisol levels compared to the group that did not receive melatonin. This study also showed that melatonin can suppress the increase in cortisol caused by exposure to light at night. Melatonin does play a role in suppressing the release of cortisol, particularly in the context of the hypothalamic-pituitary-adrenal (HPA) axis regulation. Melatonin has a known role in inhibiting the CRH-induced release of ACTH and cortisol.[13] This suppression occurs because melatonin receptor activation suppresses adrenocorticotropin (ACTH) production via BMP-4 action by pituitary At T20 cells. Since adrenocorticotropic hormone (ACTH) prompts the adrenal glands to release cortisol, suppressing ACTH production effectively suppresses cortisol release.

Under standard conditions, the influence of the HPA axis (and thus cortisol) is inversely regulated by melatonin. When melatonin levels are low (such as during morning light exposure), the HPA axis can exert its effects. Likewise, exposure to evening light suppresses melatonin, which can stimulate nighttime HPA activation to promote wakefulness. This disruption (altered timing of light exposure leading to depressed melatonin levels) results in increased cortisol during the night.[13]

The effect of melatonin on anxiety like behaviour of rat induced light at night

Animals tend to avoid open areas (the center) because they feel threatened. If animals spend more time and stay longer in the central area, this indicates increased exploration and reduced anxiety (anxiolytic). Conversely, if animals only circle around the edge of the arena (thigmotaxis) and rarely or never enter the central area, this may indicate anxiety or anxiogenic effects.

Center time was defined as the total duration spent by the animal in the central area of the open-field arena, with longer durations indicative of reduced anxiety-like behavior. Center entries represented the frequency with which the animal entered the central area, where higher entry counts were associated with lower anxiety levels. Line crossings were used as a measure of locomotor activity and exploratory behavior within the arena; increased line crossings reflected greater activity and lower anxiety-like responses. All behavioral parameters were normally distributed across experimental groups, as confirmed by the Shapiro–Wilk test ($p > 0.05$).

Table 2. Open field test parameter data of control and treatment group, obtained from any-maze software

Group	centre entries (mean ± SEM)	centre time (mean ± SEM)	line crossing (mean ± SEM)	Description
Control	9.8 ± 4.12	60.66 ± 37.52	15 ± 6.17	Anxiolitik
Dimlight	3.8 ± 1.62	8.64 ± 5.45	6.8 ± 2.70	Anxiogenik
Dimlight + Mel	12 ± 1.095	145.76 ± 74.54	22 ± 4.66	Anxiolitik
CLE	12.6 ± 2.76	131.56 ± 71.21	21.20 ± 4.12	Anxiogenik
CLE + Mel	14.8 ± 3.92	104.8 ± 42.42	25.2 ± 5.64	Anxiolitik

As shown in Figure 2A, the mean number of center entries was reduced in the dim light–exposed group compared to the control group. However, rats in the dim light + melatonin group exhibited a higher frequency of center entries than those without melatonin treatment, with a significant difference between the dim light and dim light + melatonin groups (Dunn's test, $p < 0.05$). Similarly, melatonin administration in the constant light exposure (CLE) group resulted in an increase in center entries, although this difference was not statistically significant (Dunn's test, $p > 0.05$). Figure 2B shows that center time was reduced in the dim light group relative to the control group and increased significantly following melatonin administration. In the CLE + melatonin group, center time increased compared to the dim light group but remained lower than in the CLE group. Notably, in the CLE group, measures indicative of reduced anxiety, including center entries and line crossings, were higher than in the dim light group. Figure 2C presents the frequency of center line crossings, which was lower in the dim light group than in the control group but increased following melatonin administration.

In the CLE group, the anxiolytic parameter (reduction in anxiety) was higher than those observed in the dim light group. Following melatonin administration, the anxiolytic-related parameters, including center

entries and line crossings, further increased. In contrast, the time spent in the center area of the OFT arena (center time) decreased despite melatonin treatment. Collectively, these findings indicate that melatonin supplementation attenuates anxiety-like behavior induced by nocturnal light exposure, as reflected by increased exploratory behavior, and suggest that this effect may be mediated through stabilization of circadian rhythms and modulation of stress-related hormonal activity, such as cortisol secretion.

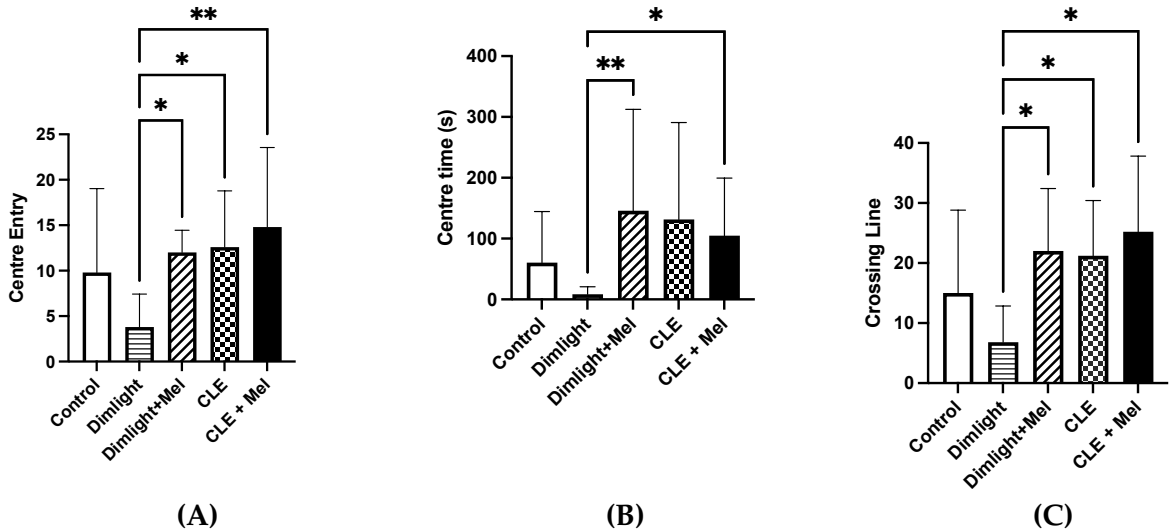

Figure 2. Open Field Test Parameter Profile. **(A)** Data Center entry with Kruskal-Wallis nonparametric test followed by Dunn's test, **(B)** Data Center times with Kruskal-Wallis test followed by Dunn's test, and **(C)** Crossing line with One Way ANOVA test followed by Fisher's LSD test. Control: Group that did not receive light exposure at night; Dimlight: Group that received dim light (5 lux) at night; CLE: Continuous Light Exposure, Group that received bright light exposure (200 lux) at night. * Significant difference ($p \leq 0.05$), ** Statistically very significant difference ($p \leq 0.01$).

Figure 3 illustrates the differences in locomotor trajectory profiles among the experimental groups. Rats in the control group exhibited active exploratory behavior throughout the Open Field Test. In contrast, the dim light and CLE groups, which were exposed to light at night, displayed trajectories indicative of heightened anxiety. The animals rarely or never entering the central area of the arena. Meanwhile, administration of oral melatonin significantly enhanced exploratory behavior and exerted anxiolytic effects, as evidenced by a higher frequency of entries into the central area compared to the dim light and CLE groups.

Light at night (LAN) exposure and disruptions to the normal light/dark cycle significantly affect anxiety-like behaviors and related physiological indicators in rat models and other nocturnal rodents.[14] Exposure of rats to constant light conditions during perinatal development resulted in increased anxiety-like behavior in adulthood.[15]

Figure 3. Representative locomotor trajectory in open field test, analyzed using ANY-mase software. (A) control group, (B) dim light group, (C) dim light-mel group, (D) CLE group, (E) CLE-mel group.

Table 3. Correlation between cortisol levels and anxiety-like behavior parameters

Dependent variable	Independent variable	Correlation test	Correlation coefficient	Sig (p-value)
Plasma cortisol	*Centre entries*	Pearson correlation	-0.280	0.175
	Centre times	Pearson correlation	-0.233	0.263
	Crossing line	Pearson correlation	-0.020	0.924

Based on the results of Pearson's correlation analysis, it was found that cortisol levels had a weak negative correlation with two anxiety-like behavior parameters, namely the frequency of entering the central area ($r = 0.280$, $p = 0.175$) and the number of crossings of the central area ($r = -0.233$, $p = 0.263$). Meanwhile, the relationship between cortisol levels and center time also showed a weak correlation ($r = -0.020$, $p = 0.924$). Although the significance test results showed insignificant results, the negative correlation between cortisol levels and center time and crossing lines reflects a tendency that increased cortisol, as an indicator of physiological stress, is associated with avoidance of open areas. This is in line with the anxiogenic behavior hypothesis, whereby animals experiencing stress tend to reduce their exploration activity in areas that are considered risky.

The effects of light at night exposure on behavior are often tied to disruptions in hormonal and nervous system regulation, particularly glucocorticoids (corticosterone in rats) and the autonomic nervous system.[14] In rats, corticosterone levels naturally peak and sharply increase in the evening, associated with the start of the daily activity period.[16] Exposure to dim light at night increases circulating glucocorticoid levels in rats and mice.[14] Retinal stimulation by light during the night modulates corticosterone production in rats. The acute corticosterone response to light at night in rats is mediated by the suprachiasmatic nuclei (SCN), possibly via the sympathetic nervous system.[16] Chronic stress (CIS) in rats significantly elevates serum corticosterone levels and increases relative adrenal weight, indicative of HPA axis activation. The reduction of these corticosterone levels, for example, through melatonin treatment, is associated with improvements in anxiety-like behaviors.[17]

Melatonin synthesis in the pineal gland is high during the night and is curtailed if light of sufficient irradiance and duration is presented to the retina during the night.[14,16] Melatonin, which is suppressed by LAN, is considered anxiolytic.[17] Chronic administration of melatonin to rats exposed to chronic immobilization stress (CIS) suppressed anxiety-like behavior. This effect was consistent with the observed reduction in relative adrenal weight and serum corticosterone levels in the melatonin-treated stressed group compared to the stressed group.[17]

Conclusions

Exposure to artificial light at night disrupts circadian rhythms, elevates cortisol levels, and induces anxiety-like behaviors in Sprague Dawley rats. The effects were more pronounced under higher light intensity. Melatonin administration reduced plasma cortisol and improved exploratory behavior, indicating its role in restoring hormonal balance and reducing anxiety. These findings suggest that melatonin mitigates the adverse neuroendocrine and behavioral effects of nocturnal light exposure and may serve as a protective agent against circadian disruption caused by artificial light at night.

Conflict of Interest

The authors report there are no competing interests to declare

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