

Long-Term Continuous Light Exposure Affects Body Weight and Blood Glucose Associated with Inflammation in Female Rats

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Abstract

Studies have indicated that night lights interfere with the circadian rhythm in the human body and threaten human health. Our previous studies indicated that continuous light exposure severely damages the reproductive endocrine system of female rats resembles polycystic ovary syndrome in women. In this study, we used the continuous measurement method to observe changes in the basal physiological indicators of female rats in an abnormal light exposure environment. Our study results indicated that in female rats: 1) the body temperature first continuously and gradually increased followed by a gradually decrease; 2) the increase in body weight slowed down at the late stage of the experimental process; 3) the random blood glucose level increased, and the fasting serum insulin level decreased; and 4) the serum C-reactive protein level increased. Our study investigated for the first time the correlation between the duration of continuous light exposure in female rats and the continuously measured basal physiological indicators and preliminarily discussed the effect of continuous light exposure on female basal metabolism and the possible inflammation mechanism. We propose that long-term continuous exposure to night lights in females severely damages their immune and metabolic systems.

Keywords

Continuous Light Exposure, Body Weight, Blood Glucose, Inflammation, Comparative Study

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#These authors contributed equally to this work.

1. Introduction

In modern society, bright lights are used at night to extend the life and production time of people; as a result, human sleep time is also greatly reduced. Many times, people exist at a sleep deprivation status, which results in many health issues, including an increase of the body mass index, cardiovascular diseases [1], diabetes mellitus, and cancer [2] [3]. Studies have shown that night lights interfere with the circadian rhythm in the human body and inhibit melatonin release [4] [5], thus causing sleep disorders in people. Females have unique physiological endocrine characteristics; therefore, they are even more sensitive to light exposure [6] [7].

It had been reported that experimental animals exposed to continuous light could present abnormal mood [8] and reduced cognitive function [9] and could be used as a hypertension animal model induced by melatonin deficiency [10]. Our previous studies showed that in a continuous light exposure environment, female rats presented deregulation of sexual cycles, polycystic ovary, hair loss, an increase in androgen, and weight loss [11]. The phenomenon of weight loss in rats suggested that this animal model may be used to represent wasting metabolic disorders. Researchers also observed pancreatic endocrine dysfunction related to the pathogenesis of polycystic ovary in rats exposed to continuous light [12]. It is necessary to study the effects of long-term continuous light exposure on the human body, especially those on female physiological functions, and the possible mechanisms of these changes to protect people from health issues resulting from elongated light exposure and/or lack of sleep and sleep rhythm disorders. Elongation of light exposure time in the environment of experimental animals can simulate the real nightlife status to study the effects of elongated light exposure in humans.

The body temperature of animals has a 24-h pattern, and the body temperature and animal activities are correlated with time [13]. Excessive light exposure can increase the body temperature of primates [14]. Therefore, body temperature monitoring can be used to understand the activity status of animals. In addition, body temperature can also reflect the inflammation status in the body. Inflammation and β -cell dysfunction in diabetes mellitus have a very close association [15]. This study aimed to understand whether gradual changes in the body temperature and blood glucose were present in the process of pancreatic function damage in animals in a continuous light exposure environment. Through monitoring of the changes in the basal indicators, such as the body temperature, body weight, and random blood glucose, in female rats in a continuous light exposure environment, we aimed to understand the correlation between the duration of continuous light exposure on female rats and these metabolism-related indicators. The effect of continuous light exposure on basal metabolism in females and the possible inflammation mechanisms were preliminarily explored.

2. Materials and Methods

2.1. Experimental Animals

The use of experimental animals in this study strictly followed the “Regulations on

management of laboratory animals of the People's Republic of China". The management of animal feeding and animal experiment manipulations conformed to the requirements of the regulations of experimental animal use of Huadong Hospital Affiliated with Fudan University and Shanghai Jiao Tong University Affiliated Sixth People's Hospital were approved. A total of 36 6-week-old, clean-grade, female SD rats were purchased from the Experimental Animal Center of the Chinese Academy of Science. The temperature of the rearing environment was 22°C - 25°C, and all rats were allowed to eat conventional feed and drink distilled water freely.

2.2. Experimental Equipment

A light exposure experiment box was specifically designed for these experiments, for which was applied China's utility model patent (patent number: ZL 2014 2 0754611.0). The length, width, and height of the box were 120 cm, 45 cm, and 180 cm, respectively. Inside, the box was evenly divided into 4 compartments from top to bottom. Each compartment could house 2 conventional animal feeding boxes. A high-efficiency shading material was used to cover the box. A layer of shade cloth was added to each compartment to ensure that the animal-raising process in each layer would not influence the other layers. Both sides of each layer were installed with ultra-quiet fans to maintain absolute air circulation in the equipment and to ensure that the temperature in internal and external environment is same. Each layer of the compartment was equipped with a fluorescent light (color temperature: 6500 K; illuminance: 600 lux) and an electronic timer switch. The duration of required light exposure time in each layer could be adjusted. **Figure 1** contains the schematic diagram of this equipment. The ear temperature was measured using an infrared ear thermometer (Omron). The blood glucose was measured using a Vigor Roche ACCU-CHEK blood glucose meter. Other equipment also included a microplate reader (Thermo, Multiskan FC, China) and an electronic balance (Sartorius, BT125D, China).

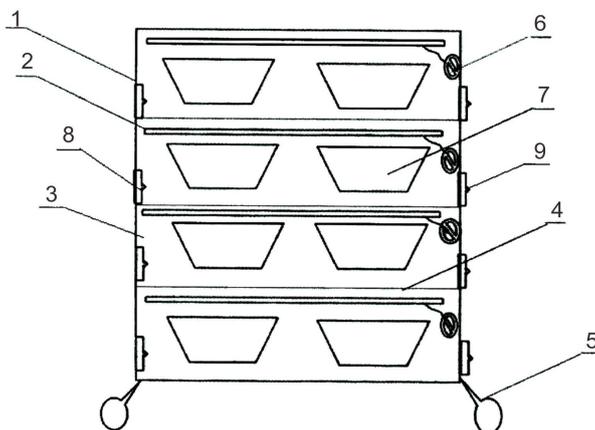


Figure 1. Schematic diagram of the light exposure experiment. 1: The light shading compartment of the experiment box (shade cloth); 2: Fluorescent lamp; 3: Single-layer experimental animal-raising box; 4: Light shading compartment (baffle); 5: Movable pulley; 6: Microcomputer-controlled switch; 7: Animal-raising box; 8: Inlet fan; 9: Outlet fan.

2.3. Grouping and Testing

A total of 36 6-week-old female SD rats were randomly divided into a control group (LD, light/dark), a light exposure group (LL, light/light) and a dark group (DD, dark/dark). Each group had 12 animals that were placed in the light exposure experiment box. The circadian rhythm of light exposure in the LD group was 12 h light/12 h dark for each cycle (light exposure started at 8:00 Beijing standard time in the morning). Rats in the LL group were exposed to a continuous light environment (24-h continuous light exposure). Rats in the DD group were placed in a 24-h dark environment. The light exposure cycle was 120 d. The body weights of the rats in each group were measured at 1 pm each day, and the ear temperature was measured using an infrared ear thermometer (Omron). The random blood glucose level was measured every 5 d; blood from the tail vein was collected at 8:00 in the morning for each time point.

2.4. Tissue Collection and Serum Detection

When the continuous light exposure cycle ended, fasting rats were deeply anesthetized by an intraperitoneal injection of 10% chloral hydrate (0.4 ml/100 g body weight). Blood was collected from the abdominal aorta and placed on a stationary shelf at 4°C for 30 min. The serum samples were separated by centrifuge (centrifuge force 2000 g, 10 min) and stored at -80°C. The serum insulin and C-reactive protein levels in the experimental animals of each group were measured using an enzyme-linked immunosorbent assay (ELISA) according to the product manual. The insulin ELISA reagent kit (cat: #EZRMI-13K) and the C-reactive protein ELISA reagent kit (cat: CYT294) were from Millipore (USA).

2.5. Statistical Methods

Data are presented as the means \pm SD. Statistical analyses of all of the data were performed using the IBM SPSS v21.0 statistical software. Comparisons of the randomly measured body weight, body temperature, and random blood glucose were performed using analysis of variance (ANOVA) of repeated measurement data. Comparison of body temperature changes before and after light exposure was examined using a paired *t* test. Comparison of tissue weights between the groups was first examined using the normality test. Data that conformed to a normal distribution were analyzed using ANOVA to compare the differences between groups. Data that did not conform to a normal distribution were analyzed using a rank sum test to compare the differences. *P* < 0.05 indicated that the difference was significant. The correlation between all of the indicators and the light exposure time was evaluated using the Pearson correlation coefficient.

3. Results

3.1. Changes in the Body Temperature of Female Rats in a Continuous Light Exposure Environment

The results of the repeated measures ANOVA in **Figure 2** show that during the 120 d

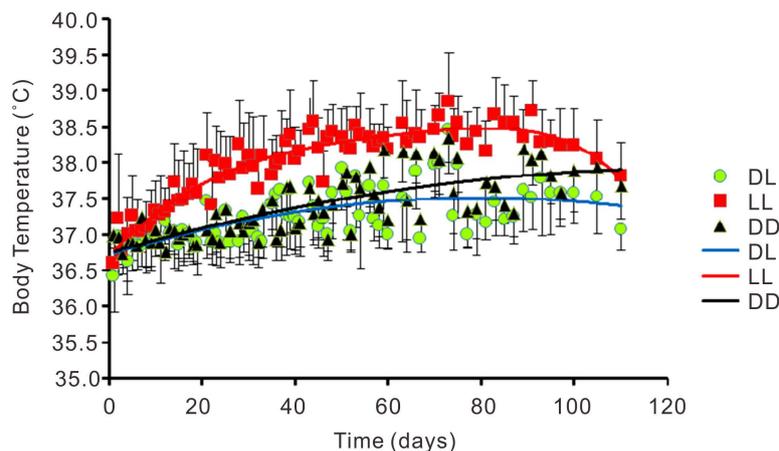


Figure 2. Comparison of repeated measures data of the body temperature of the experimental animals ($n = 12$ in each group).

of the continuous experiment, the body temperatures of animals in the LL, LD, and DD groups had significant differences. Pairwise comparison between 2 groups and pairwise comparison among the overall groups showed that the body temperature in the LL group significantly increased. The continuously measured body temperature was significantly different between the LL and LD groups ($P = 0.000008$, $n = 12$ each group). The continuously measured body temperature was also significantly different between the LL and DD groups ($P < 0.000001$, $n = 12$ each group). Although the continuously measured body temperature values in the DD group showed an increasing trend, there was no statistical significance compared with those in the LD group ($P = 0.685563$, $n = 12$ each group). A further segmented comparison showed that after 10 d of light exposure, the body weight in the LL group increased significantly ($37.32^{\circ}\text{C} \pm 0.42^{\circ}\text{C}$ versus $36.89^{\circ}\text{C} \pm 0.20^{\circ}\text{C}$, $P = 0.004445$, $n = 12$) and was higher than that in the LD group. After that, the body temperature gradually increased. The maximum average body temperature in the LL group reached $38.82^{\circ}\text{C} \pm 0.382^{\circ}\text{C}$ (on the 73rd d of light exposure). Subsequently, the body temperature in the LL group decreased gradually. The average body temperatures on the 120th d and 90th d (1 month before the end of continuous light exposure) of light exposure in the LL group were compared using a paired t test, and the results showed that the decrease in average body temperature on the 120th day had a significant difference ($37.783^{\circ}\text{C} \pm 0.482^{\circ}\text{C}$ versus $38.36^{\circ}\text{C} \pm 0.39^{\circ}\text{C}$, $P = 0.000263$; $n = 12$).

3.2. Changes in the Body Weight of Female Rats in a Continuous Light Exposure Environment

The overall changes of the average body weights of rats within the LL, LD, and DD groups during the 120 d of the continuous experiment were compared using repeated measures ANOVA. The result did not reveal a significant difference ($P = 0.158$; $n = 12$ each group). However, the change curve showed that the body weight of rats in the LL group at the late stage of model establishment was significantly lower than those in the

other 2 groups. Therefore, the differences between groups at different time points were independently compared. The comparison results showed that the body weights of rats in all of the groups did not have significant differences within 70 d of continuous light exposure; the p-values were all larger than 0.05. After 70 d of continuous light exposure, the increase in rat body weight in the LL group significantly slowed down (on the 70th day: LL group versus LD group was 279.06 ± 20.82 g versus 294.78 ± 15.39 g; $P = 0.016049$; $n = 12$ in each group). The body weights between the DD and LL groups were not significantly different. On the 120th d of continuous light exposure, the difference of the body weights between the LL group, the LD and DD groups was even more significant (Figure 3).

3.3. Changes in the Random Blood Glucose of Female Rats in a Continuous Light Exposure Environment

The repeated measures ANOVA results showed that the comparison of the overall random blood glucose among the 3 experimental groups revealed a significant difference; the p value was 0.003. The pairwise comparison results showed that compared to that in the LD group, the blood glucose levels in the LL group (LL group versus LD group: 6.14 ± 0.33 mmol/L versus 5.57 ± 0.32 mmol/L; $P = 0.0039170$; $n = 12$ in each group) and the DD group (DD group versus LD group: 6.15 ± 0.36 mmol/L versus 5.57 ± 0.32 mmol/L; $P = 0.001475$; $n = 12$ in each group) both increased; the results were significantly different. The random blood glucose levels between the DD and LL groups were not significantly different ($P = 0.523647$). A segmented comparison between groups showed that there were significant differences in some scattered time points; the presence of differences did not have significant time variations (Figure 4).

3.4. Increase in Serum C-Reactive Protein and Decrease in Fasting Serum Insulin Levels in Female Rats Exposed to Continuous Light

The levels of fasting serum insulin and serum C-reactive protein in rats of each group

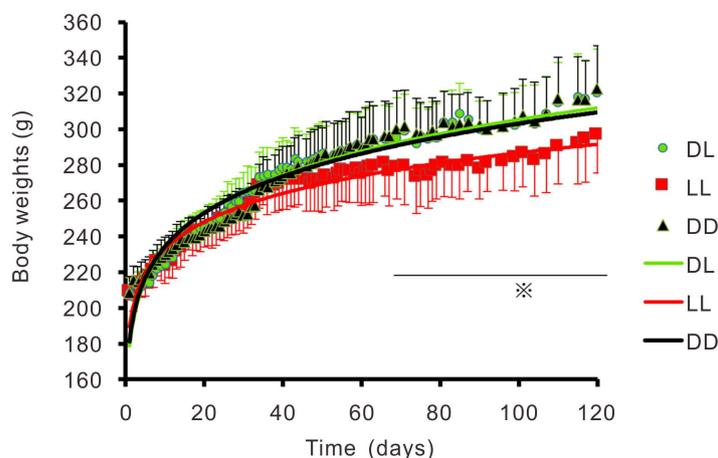


Figure 3. Comparison of repeated measures data of the body weight of the experimental animals (* $P < 0.05$ compared to the LL group, $n = 12$ in each group).

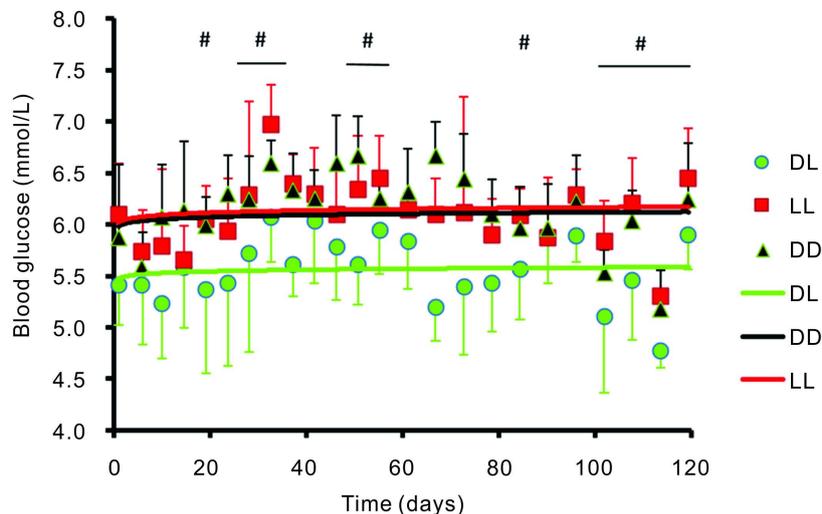


Figure 4. Comparison of repeated measures data of the random blood glucose in the experimental animals (# $P < 0.05$ compared to the LD group, $n = 12$ in each group).

after the end of 120 d of light exposure were detected and compared. The results showed that compared to those in the LD group, the insulin levels in the LL group significantly decreased (0.55 ± 0.025 ng/ml versus 0.77 ± 0.0441 ng/ml, $P = 8.11479E-4$; $n = 12$ in each group). The insulin levels in the DD group also significantly decreased and were lower than those in the normal control (0.62 ± 0.03 ng/ml LL versus 0.766 ± 0.04 ng/ml, $P = 0.02144$; $n = 12$ in each group) (Figure 5(a)). The results of the comparison of the serum C-reactive protein levels showed that compared to that in the LD group, the level in the LL group significantly increased (19.13 ± 2.48 μ g/L versus 28.53 ± 2.85 μ g/L, $P = 0.015629$; $n = 12$ in each group); the difference was significant. The difference between the DD and LD groups was not significantly different (23.42 ± 3.06 μ g/L versus 28.53 ± 2.85 μ g/L, $P = 0.307159$; $n = 12$ in each group) (Figure 5(b)).

3.5. Correlational Analysis between Body Temperature, Body Weight, and Blood Glucose Changes in Female Rats after Continuous Light Exposure and the Light Exposure Time

The body weight of rats in the LL group was significantly higher than those in the LD and DD groups. The Pearson correlation examination showed that the body temperature changes in rats of the LL group correlated with the duration of light exposure (Pearson correlation coefficient 0.661, $P = 0.000439$) and that the body temperature changes in rats of the LL group correlated with the body weight changes (Pearson correlation coefficient 0.787, $P = 0.000005$). Although the blood glucose in rats of the LL group significantly increased after light exposure, there was no significant correlation between the increase in blood glucose and the light exposure time ($P = 0.962$), and blood glucose did not increase with the increase in the light exposure time. The changes in blood glucose did not significantly correlate with body temperature and body weight (body temperature: $P = 0.586$; body weight: $P = 0.357$) (Table 1).

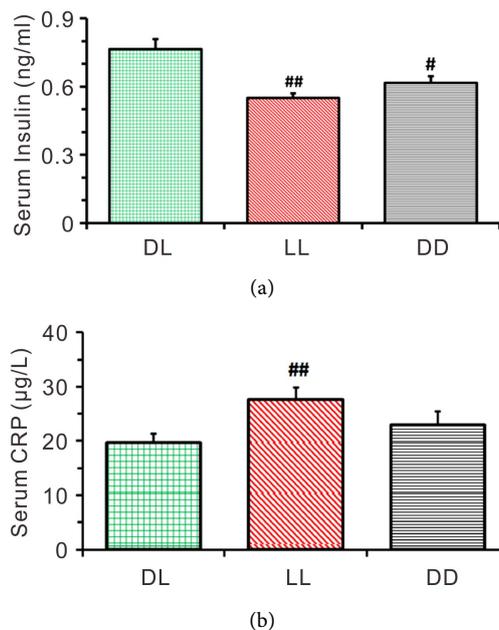


Figure 5. Comparison of the fasting serum insulin levels and serum C-reactive protein levels after the end of continuous light exposure. (a) The comparison of the fasting serum insulin levels in the rats of each group after 120 d of continuous light exposure. (b) The comparison of serum C-reactive protein levels in three group (# $P < 0.05$ compared to the LD group; ## $P < 0.01$ compared to the LD group; $n = 12$ in each group).

Table 1. Correlational analyses of light exposure time, body temperature, body weight, and blood glucose in the LL group.

		Light exposure time	Body temperature	Body weight	Blood glucose
Light exposure time	Pearson correlation	1	0.661**	0.915**	-0.020
	P value		0.000	0.000	0.926
Body temperature	Pearson correlation	0.661**	1	0.787**	0.117
	P value	0.000		0.000	0.586
Body weight	Pearson correlation	0.915**	0.787**	1	0.197
	P value	0.000	0.000		0.357
Blood glucose	Pearson correlation	-0.020	0.117	0.197	1
	P value	0.926	0.586	0.357	

** $P < 0.01$.

4. Discussion

Through changes in the light exposure environment of female rats, this study observed, for the first time, changes in basal physiological indicators, such as body temperature,

body weight, and random blood glucose, with the elongation of continuous light exposure time. This study aimed to understand the correlation between the duration of continuous light exposure and these metabolism-related indicators and to preliminarily investigate the influences of continuous light exposure on the basal metabolism of females and possible inflammation mechanisms. Our results showed that after chronic continuous light exposure in female rats: 1) the body temperature first continuously and gradually increased followed by a gradually decrease; 2) the increase of body weight slowed down at the late stage of the experimental process; 3) the random blood glucose level increased, and the fasting serum insulin level decreased; and 4) the serum C-reactive protein level increased.

Working under lights at night has adverse influences on reproductive functions [16]. Our previous studies already showed that female rats had hyperandrogenism and polycystic ovary changes after long-term light exposure [11]. Continuous light exposure induced a decrease in the endocrine secretion function of the pancreas [12]. We were interested in the changes in the physiological status in the body following the resultant damage from the long-term process. Similar light exposure caused an increase in body temperature in primates [14]. Our current study showed that after 10 d of continuous light exposure, the body temperature of the rats already demonstrated significant differences between the groups. Although the increase of body temperature in the animals significantly correlated with their activities, light pollution induced an increase in the core body temperature that did not correlate with activities [14]. The continuous light exposure caused the disappearance of the circadian rhythm in rats and maintained the rats at a 24-h continuous state of activity [17]; however, the 24-h total activity amount was inhibited by light stimulation [18]. We previously observed the phenomenon of reduced activity in rats after 16 w of light exposure, which also confirmed this point [11]. Other studies also showed that the body temperature of mice increased at night after being exposed to light at night; in addition, the expression of pro-inflammatory cytokines also increased [19]. This study showed that with the increase in light exposure time, rats presented a gradual increase in body temperature, which could reach a high temperature of approximately 38.8°C. After the temperature was maintained for approximately 2 months, it gradually decreased. These changes correlated with the light exposure time. Although the regulation of the circadian rhythm of motion and the regulation of the circadian rhythm of body temperature may occur through 2 types of pathways [20], the serum C-reactive protein level in rats of the light exposure group increased compared to that of the normal group; the body temperature did not increase in a dark environment and was consistent with changes in the C-reactive protein level. These results reflected the correlation between body temperature and inflammatory responses. In contrast, the circulating white blood cell count and phenotype, lymphocyte metabolism and function, and cytokines had a significant circadian rhythm [21]. Under a complete dark environment or an alternating light and dark environment, changes in rat melatonin were not significantly different; however, in a continuous light exposure environment, the melatonin levels decreased significantly [22]. Night lights

inhibited the functions of cellular immunity and humoral immunity [23]-[25]. This study showed that body temperature increased, accompanied by a significant increase in the serum C-reactive protein level. These results indicated that continuous light exposure induced the increase in body temperature in female rats through immune and inflammatory responses.

The blood glucose level was determined by the balance between glucose intake (diet and glycogen synthesis) and consumption (skeletal muscle, cardiac muscle, and adipose tissue metabolism). It was reported that genetically modified mice with clock gene mutations presented a significant increase in hepatic adipocytes, glycogen accumulation, hypercholesterolemia, hypertriglyceridemia, hypoinsulinemia, and hyperglycemia [26]. Our study showed that a significant decrease in the serum fasting insulin level occurred in light exposure or a dark environment after 120 d, which confirmed the influence of the disappearance of the circadian rhythm on pancreatic functions. There may be 3 reasons for this effect. On one hand, the increase of blood glucose was associated with changes in the melatonin level because night lights can inhibit the melatonin level [27]. On the other hand, studies showed that rats in a continuous light exposure environment do not present all phenomena of biological clock disorders; thus, the increase in blood glucose may be associated with changes in an anxiety-like mood in rats [8] [28]. Continuous exposure of rats to dim lights from birth to 9 weeks old increased anxiety-like behavior [28]. The third reason was the abnormal regulation of glucose metabolism by the liver. Night lights could interfere with the biological clock rhythm of the liver [29]. Previous studies showed that a large amount of proteins in liver tissues associated with core physiological functions of the liver all presented a significant circadian rhythm [30]. Therefore, chronic continuous light exposure damages the endocrine metabolism functions of female rats.

Decrease in body weight induced by light exposure correlated with an increase in body temperature.

Studies have shown that an increase in light exposure in animals affects metabolism and increases body weight [29] [31]-[33]. Our study results showed that the body weights of female rats in the light exposure group and the control group were not significantly different within 70 d of continuous light exposure; however, the observed body weight increase of the light exposure group significantly decreased after 70 d of continuous light exposure. The analytical results showed that when comparing previous studies showing an increase in body weight by prolonged light exposure [29] [34] [35] and our study, differences were revealed in the rat strains, light exposure time, and light illumination, which may be causative reasons for the differences in the study results. However, continuous light exposure could also change the nocturnal activities of normal rats [36]. Although rats exhibited activity for 24 h in a light exposure environment, the overall activity was inhibited [14]; in addition, night lights caused a decrease in food intake by rats [34]. Furthermore, eating in a night light environment is a non-regular nocturnal activity of rodents, which may increase abnormal metabolism [37]. This may also be another reason why the body weight of female rats exposed to continuous light

decreased compared to that in rats exposed to normal light or continuous dark environment in our study. Third, the activity of retinal ganglion cells had a circadian rhythm under a dim light environment [38]. At the time point around the dark/light change, the animals had increased rapid eye movement sleep, whereas the sleep time or balance were not changed significantly [32]. However, our study was conducted in a continuous light exposure environment; there was no light/dark alternating point. The influences of continuous light exposure and dim night light on the circadian rhythm may be different, which may also cause the differences in body weight and metabolism. Fourth, our correlation studies showed a significant correlation between changes in body weight and body temperature. In addition, the increase in body temperature preceded the decrease in body weight. The increase in body temperature is a reflection of inflammatory responses; therefore, inflammatory responses may also influence body weight.

A gradual increase and loss in body temperature, persistent hyperglycemia, inhibition of increase in body weight, and decrease in insulin levels are important characteristics of the physiological influences on female rats mediated by long-term continuous light exposure. The changes in the body temperature and body weight of female rats during the continuous chronic light exposure process correlated with the duration of light exposure and elevated C-reactive protein; however, there was no correlation between the increase in random blood glucose and the duration of light exposure. Our study results imply that long-term continuous light exposure severely damages the immune and metabolic systems of females. The health concept of “going out for work at sunrise and resting at sunset” from ancient China has important practical significance in modern society with exposure to bright lights.

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