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# Bright Light Therapy Increases Blood Pressure and Changes the Structure of Circadian Rhythm of Melatonin Secretion in Spontaneously Hypertensive Rats

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Phototherapy (therapy with bright light) is widely used to treat seasonal affective disorders, different types of depression, sleep disorders, and other diseases; it has no significant contraindications, but its effects on functional state and biological rhythms of the cardiovascular system in hypertension are poorly studied. In experiments on Wistar-Kyoto and SHR (spontaneously hypertensive rats) rats, the effect of bright light therapy on the daily profile of BP, HR, and production of epiphyseal melatonin was investigated. Phototherapy was simulated by exposure to 9000-lux cold light at the level animal eyes over 1 h (from 10.00 to 11.00 h) with LED lamps. In freely moving rats (free access to food), daily profiles of BP and HR were studied by 24-h continuous telemetry monitoring. The production of epiphyseal melatonin was assessed by measuring urinary concentration of its stable metabolite 6-sulfatoxymelatonin (aMT6s) during the day and night. During phototherapy, systolic BP significantly increased in in animals of both lines and diastolic BP increased in SHR rats. This effect persisted after the end of phototherapy session. Bright light had no effect on HR. In Wistar-Kyoto rats, phototherapy induced a significant decrease in daily concentration of aMT6s, but its nocturnal level did not change. In SHR rats, bright light therapy significantly decreased nighttime concentration of aMT6s in the urine and had no effect on daytime concentration of this metabolite. As a result, the difference between the night and day levels of aMT6s in the urine was leveled. Phototherapy produced more pronounced and less favorable effect on animals with primary arterial hypertension.

**Key Words:** *bright light therapy; arterial hypertension; biological rhythms; melatonin*

Over 30 years, phototherapy (therapy with bright light) has been used as one of the effective therapies for seasonal affective disorders, bipolar disorders, seasonal and non-seasonal depression, prenatal and postpartum depression, sleep disorders and other diseases, both in the form of monotherapy and an additional method treatment [8,11,12,14]. Phototherapy is also used in the treatment of eating disorders and obesity [4,5]. The mechanisms that mediated the influence of bright light on the CNS can be associated with the "biological clock" responsible for synchronization of circadian rhythms with photoperiod parameters [9]. The central regulatory elements of "biological clock" are the suprachiasmatic nuclei (SCN) of the hypothalamus and the pineal gland. The coordination of endogenous biological rhythms with external natural rhythms is realized mainly due to the reactions of these brain structures to light exposure. Light is the main timekeeper for "biological clock" influencing the parameters of own circadian rhythms [10]. The effects of light are mediated by a third type of photoreceptor

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in the retina of mammals called internal photosensitive retinal ganglion cells (ipRGC) [6,7]. The structure of endogenous rhythms depends not only on the features of the photoperiod determined by the durations of the light and dark phases of the day. A significant role in these rhythm-dependent processes is played by the quality of light (brightness, spectral characteristics, *etc*.).

There are several theories that explain the mechanisms of action of bright light. According to the theory of phase shift, light with certain characteristics can change the phases of biorhythms in animals and humans and resynchronize them in case of a disorder. The melatonin theory puts in the first place the process of secretion of epiphyseal melatonin [13]. The dynamics of changes in the secretion of melatonin, as the main mediator of functioning of "biological clock", during bright light therapy is, therefore, of particular interest. Despite the fact that phototherapy has no significant contraindications, its effect on the functional state and biological rhythms of the cardiovascular system remains poorly understood. At the same time, many patients with seasonal affective disorders, different types of depression, sleep disorders, *etc*., can also have certain concomitant diseases, in particular arterial hypertension of different origins.

Our aim was to determine the effect of bright light therapy on circadian profile of BP, HR, and epiphyseal melatonin production under normal conditions and in primary (genetically determined) arterial hypertension in an animal experiment.

## MATERIALS AND METHODS

The experiments were performed on adult male SHR (spontaneously hypertensive rats) and Wistar-Kyoto rats (rats with normal BP). The animals were kept and experiments were performed in accordance with the Order No. 755 of the USSR Ministry of Health (August 12, 1977) and the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, 1986).

In the first series of experiments (SHR, $n$=5; Wistar-Kyoto, $n$=5), 24-h recording of BP and ECG in standard lead II was performed by using telemetry monitoring system. In the second series (SHR, $n$=5; Wistar-Kyoto, $n$=5), the production of epiphyseal melatonin was evaluated by the urinary concentration of its stable metabolite 6-sulfatoxymelatonin (aMT6s) by ELISA.

In both series of experiments, the animals were kept under conditions of artificial illumination with 12/12 h light/dark phase ratio (light from 07.00 to 19.00 h). Illuminance in the light phase of the day was 350 lx at the level of animals eyes and in the dark phase <0.5 lx. During the experiments, the animals were kept in individual cages (during telemetric monitoring) or in individual metabolic cages (during urine collection for aMT6s assay). The room temperature was maintained at 23°C; food was given at the same time of the day (19.00 h).

Therapy with bright light was conducted by exposure to cold light with a brightness of 9000 lux at the level of animal eyes over 1 h (from 10.00 to 11.00 h) with LED lamps.

All studied parameters were recorded on the day of bright light therapy and on the previous day when exposure to bright light was not applied (control).

Continuous 24-h (07.00-07.00 h) registration of BP, ECG in standard lead II was conducted using Data Sciences International equipment. To this end, DSI HD-S11 radio transmitters (devices that monitor BP, cardiac biopotentials and transmit a signal to special radios in the form of a radio signal) were implanted to the animals under general anesthesia. Registration of BP was conducted via a catheter introduced into the abdominal aorta and fixed with tissue hemostatic adhesive. The electrodes for ECG monitoring were fixed under the chest muscles in the projection of the electrical axis of the heart. Recordings of all parameters began in 10 days after implantation of the radio transmitters. Thus, the animals during the experiment mover freely and had free access to food.

All data were stored in computer memory and processed using Dataquest A.R.T. 4.2 Gold. The following parameters were evaluated: mean over 24 h (07.00-07.00 h), mean daytime (07.00-19.00 h), and mean nighttime (19.00-07.00 h) systolic BP ($sBP_{24h}$, $sBP_{day}$, $sBP_{night}$), diastolic BP ($dBP_{24h}$, $dBP_{day}$, $dBP_{night}$), and HR ($HR_{24h}$, $HR_{day}$, $HR_{night}$). In addition, sBP, dBP, and HR were evaluated from 10.00 to 11.00 h (the period of exposure to bright light) and at the same time on the day before exposure to bright light (sBP 10-11 h, dBP 10-11 h, HR 10-11 h).

The study of the rhythm structure of BP and HR was conducted on the basis of non-linear analysis, which is a combination of partial Fourier analysis with step-by-step regression using the Chronos-Fit program [15]. The following parameters were determined: mesor (mean level of the studied parameter over a 24-h period), amplitude (maximum deviation of the studied parameter from the mesor), amplitude of oscillations (difference between the maximum and minimum values of the studied parameter), power of oscillations (% of rhythm; chronobiological parameter that characterizes the fraction of the oscillatory processes, the fraction of the values of the studied parameter characterized by oscillatory pattern of distribution over 24 h).

Urine excreted during the day (07.00-19.00 h) and night (19.00-07.00 h) periods was collected using

AE0906 metabolic chambers (Open Science), and the content of aMT6s was measured using ELISA kit for 6-Sulfatoxymelatonin (Buhlmann Laboratories AG). The concentration of aMT6s is in direct correlation with the total level of melatonin in the blood [1-3].

Statistical processing of the results was conducted using Statistica 6.0 (StatSoft, Inc.). For each parameter, the mean and error of the mean were calculated. Significance of the results was assessed using the Mann—Whitney *U* test (the difference between the mean values at $p \leq 0.05$ was taken as significant).

## RESULTS

**Telemetry monitoring of BP and HR.** Analysis of the results of telemetric monitoring of BP and HR in animals of both groups revealed (Table 1) a significant increase in sBP during phototherapy in comparison with the same time interval (from 10.00 to 11.00 h) on the previous day in both normotensive and SHR rats and a significant increase in the mean daytime sBP on the day of phototherapy, which probably suggests that the effects of bright light persisted after the end of exposure. During nighttime, no significant differences in this parameter were observed. In SHR rats, dBP also increased during the exposure to bright light, but its mean daytime level had only a tendency to increase. It should be noted that phototherapy produced no significant effect on HR at all analyzed intervals in normotensive and hypertensive rats. This observation suggests that BP elevation under the influence of phototherapy is not a result of stress reaction, but is mediated by other mechanisms.

Nonlinear analysis of the data telemetric monitoring of BP and HR in normotensive Wistar-Kyoto rats showed (Table 2) that the mesor of sBP, dBP and HR after exposure to bright light did not differ from the control; the amplitude of dBP, HR, and the range of HR fluctuations significantly increased after phototherapy in comparison with the control. Therefore, exposure to bright light in normotensive rats led to some changes in the structure of BP and HR rhythms, which can be interpreted as reactions aimed at strengthening of the adaptive capacities of the cardiovascular system.

In SHR rats, analysis of the mesor showed the same picture as in normotensive animals. Phototherapy had practically no effect on the mesor of sBP, dBP and HR. However, the range, amplitude, and power of sBP, dBP and HR fluctuations during bright light therapy did not significantly differ from the control.

Thus, the structure of circadian rhythms of these functions in SHR rats is characterized by a more pronounced resistance to bright light than in normotensive animals.

**Secretion of epiphyseal melatonin.** The level of epiphyseal melatonin was evaluated by the concentration of aMT6s in the urine (Table 3). In normotensive rats under standard light regime without exposure to bright light, a distinct circadian rhythm of aMT6s concentration in the urine was observed with a predominance of nighttime values over daytime ones. This rhythm persisted during daytime in animals exposed to bright light. During phototherapy, a statistically significant decrease in the daytime concentration of aMT6s was determined, however, nighttime level of aMT6s did not change. In SHR rats kept at 12/12 h illumina-

**TABLE 1.** BP and HR in Wistar-Kyoto and SHR Rats Exposed to Bright Light for 1 h (*M*±*m*)

| Parameter | Wistar-Kyoto rats | | SHR rats | |
|---|---|---|---|---|
| | 12/12 h | 12/12 h+bright light 1 h | 12/12 h | 12/12 h+bright light 1 h |
| $sBP_{24h}$, mm Hg | 112.45±0.93 | 116.66±2.39 | 185.25±3.83 | 192.13±4.93 |
| $dBP_{24h}$, mm Hg | 82.84±4.36 | 86.17±6.13 | 131.09±4.36 | 138.31±5.39 |
| $HR_{24h}$, bpm | 225.48±3.51 | 224.13±2.73 | 272.03±3.86 | 276.71±3.58 |
| $sBP_{day}$, mm Hg | 109.43±0.77 | 116.78±3.00* | 173.82±3.57 | 186.19±4.75* |
| $dBP_{day}$, mm Hg | 80.24±4.09 | 87.3±6.67 | 122.68±3.89 | 133.92±4.94 |
| $HR_{day}$, bpm | 214.72±4.04 | 206.6±1.99 | 242.84±2.84 | 247.71±3.38 |
| $sBP_{night,}$ mm Hg | 114.95±1.52 | 116.54±2.07 | 196.65±4.27 | 197.92±5.25 |
| $dBP_{night,}$ mm Hg | 85.14±4.79 | 85.04±5.67 | 139.46±4.92 | 142.58±5.94 |
| $HR_{night,}$ bpm | 232.31±3.98 | 241.69±4.61 | 301.01±5.96 | 304.87±4.20 |
| sBP 10-11 h, mm Hg | 107.57±2.35 | 117.65±2.85* | 182.98±2.57 | 195.09±3.18* |
| dBP 10-11 h, mm Hg | 77.56±2.73 | 86.95±6.31 | 128.53±3.39 | 140.79±3.61* |
| HR 10-11 h, bpm | 214.07±3.59 | 203.17±5.99 | 247.00±4.08 | 260.71±6.12 |

**Note.** Here and in Table. 2: *$p \leq 0.05$ in comparison with standard light mode (12/12 h).

**TABLE 2.** Parameters of 24-h Profile of sBP, dBP, and HR Determined on the Basis of Nonlinear Analysis in Wistar-Kyoto and SHR Rats Exposed to Bright Light for 1 h (*M*±*m*)

| Parameter | Wistar-Kyoto rats | | SHR rats | |
|---|---|---|---|---|
| | 12/12 h | 12/12 h+bright light 1 h | 12/12 h | 12/12 h+bright light 1 h |
| Mesor | | | | |
| sBP, mm Hg | 112.37±0.94 | 116.74±2.33 | 180.19±7.42 | 187.75±6.43 |
| dBP, mm Hg | 82.79±4.41 | 86.32±6.11 | 131.72±4.28 | 138.59±5.40 |
| HR, bpm | 225.09±3.74 | 224.01±2.79 | 272.63±4.03 | 276.88±3.47 |
| Amplitude | | | | |
| sBP, mm Hg | 8.09±1.97 | 11.35±1.91 | 17.76±2.76 | 16.22±2.95 |
| dBP, mm Hg | 7.67±0.06 | 11.12±0.07* | 15.41±3.34 | 15.69±3.02 |
| HR, bpm | 34.37±4.95 | 60.4±2.76* | 66.08±7.86 | 56.67±7.89 |
| Range | | | | |
| sBP, mm Hg | 15.94±3.67 | 22.18±3.67 | 35.51±5.51 | 30.63±4.67 |
| dBP, mm Hg | 15.32±2.62 | 21.26±3.39 | 30.12±6.30 | 28.00±4.78 |
| HR, bpm | 61.53±3.97 | 103.32±3.5* | 111.54±9.95 | 103.18±8.58 |
| Power of oscillations (% of rhythm) | | | | |
| sBP, % | 24.82±5.41 | 27.28±3.8 | 35.48±5.04 | 25.29±5.29 |
| dBP, % | 28.82±5.34 | 33.03±4.11 | 32.69±6.81 | 30.51±6.22 |
| HR, % | 53.43±5.27 | 64.59±2.92 | 71.84±2.10 | 70.63±2.85 |

**TABLE 3.** Urinary Concentration of aMT6s in Wistar-Kyoto and SHR Rats Exposed to Bright Light for 1 h (ng/ml; *M*±*m*)

| Time period | Wistar-Kyoto rats | | SHR rats | |
|---|---|---|---|---|
| | 12/12 h | 12/12 h+bright light 1 h | 12/12 h | 12/12 h+bright light 1 h |
| Day | 25.5±1.49 | 17.04±1.67* | 16.27±1.23 | 19.10±3.79 |
| Night | 32.74±2.78$^{+}$ | 29.39±1.58$^{+}$ | 30.37±2.54$^{+}$ | 19.01±4.21* |

**Note.** $p \leq 0.05$ in comparison *with standard illumination regime (12/12 h), $^{+}$with daytime values.

tion regime without exposure to bright light, similar to Wistar-Kyoto rats, the daytime level of aMT6s in the urine was significantly lower than at night. After bright light therapy, nighttime concentration of aMT6s in the urine significantly decreased and daytime concentration did not change. As a result, the difference between the night and daytime levels of aMT6s in the urine disappeared.

Based on these results, we can conclude that phototherapy induced different changes in the production of epiphyseal melatonin in normotensive and hypertensive animals. Animals with normal BP maintained the circadian rhythm of melatonin secretion, but with a decrease in its daytime concentration. In animals with high BP, a decrease in the nighttime concentration of epiphyseal melatonin and, as a consequence, disappearance of the circadian rhythm of its production were observed.

Thus, exposure to bright light in the used phototherapy mode induced an increase in sBP in normotensive and SHR rats and additionally an increase in diastolic BP in SHR rats. Under the influence of bright light, some changes in the rhythmic parameters of BP and HR were observed in normotensive rats, but not in hypertensive animals. In hypertensive animals, the circadian rhythm of melatonin secretion disappeared due to a decrease in its nocturnal production. In normotensive rats, no disturbances in the rhythm of melatonin production were observed. In general, phototherapy produced more pronounced and less favorable effect on the body of animals with primary arterial hypertension.

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