Suppression of Blue Light at Night Ameliorates Metabolic Abnormalities by Controlling Circadian Rhythms

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PURPOSE. Light-emitting diodes that emit high-intensity blue light are associated with blue-light hazard. Here, we report that blue light disturbs circadian rhythms by interfering with the clock gene in the suprachiasmatic nucleus (SCN) and that suppression of blue light at night ameliorates metabolic abnormalities by controlling circadian rhythms.

METHODS. C57BL/6J mice were exposed to 10-lux light for 30 minutes at Zeitgeber time 14 for light pulse with blue light or blue-light cut light to induce phase shift of circadian rhythms. Phase shift, clock gene expression in SCN, and metabolic parameters were analyzed. In a clinical study, healthy participants wore blue-light shield eyewear for 2 to 3 hours before bed. Anthropometric data analyses, laboratory tests, and sleep quality questionnaires were performed before and after the study.

RESULTS. In mice, phase shift induced with a blue-light cut light pulse was significantly shorter than that induced with a white light pulse. The phase of Per2 expression in the SCN was also delayed after a white light pulse. Moreover, blood glucose levels 48 hours after the white light pulse were higher than those after the blue-cut light pulse. Irs2 expression in the liver was decreased with white light but significantly recovered with the blue-cut light pulse. In a clinical study, after 1 month of wearing blue-light shield eyeglasses, there were improvements in fasting plasma glucose levels, insulin resistance, and sleep quality.

CONCLUSIONS. Our results suggest that suppression of blue light at night effectively maintains circadian rhythms and metabolism.

Keywords: blue light, circadian rhythm, metabolism

There is accumulating evidence of a close association between metabolism and sleep.1–3 An increase in social jet lag and blue-light exposure at night in modern society indicates that circadian misalignment and sleep disorders have emerged as significant health problems. Light-emitting diodes (LEDs) emit high intensities of blue wavelengths of light that are associated with blue-light hazard. Blue-light reduction at night may be beneficial for better sleep quality4; however, its effects on metabolism have not yet been investigated.

Light is the most important stimulus for regulating circadian and behavioral systems.5 It synchronizes the circadian clock to the solar day and regulates sleep. Therefore, irregular light exposure impairs circadian rhythms and sleep. Exposure of mice to brief light stimuli during their nocturnal active phase induces several simultaneous behavioral and physiological responses, including circadian rhythm phase shifts and changes to circadian rhythms.

The suprachiasmatic nucleus (SCN) is a core component of the circadian timing system. The circadian clock genes (period [Per]1, Per2, cryptochrome [Cry]1, Cry2, Clock, and Bmal1) in SCN give rise to a rhythm with a period of approximately 24 hours by means of transcription–translation feedback loops.6–9 Importantly, the circadian clock gene network plays a significant role in mammalian energy balance. Clock mutant mice have a greatly attenuated diurnal feeding rhythm, are hyperphagic and obese, and develop a metabolic syndrome of hyperlipidemia, hyperglycemia, and hypoinsulinemia.10 Moreover, Cry-null mice show salt-sensitive hypertension due to abnormally high synthesis of the mineralocorticoid aldosterone by the adrenal gland.11

Disruption of sleep is a risk factor for cardiovascular12 and immunologic13 dysfunction in humans. People who have difficulties initiating sleep and nonrestorative sleep have a significantly increased risk of cardiovascular mortality compared with those without such symptoms.14 Similarly, patients with poorly controlled asthma took longer to fall asleep, awoke more often, and spent more time awake during the night compared to those with well-controlled asthma.15

In this study, we aimed to evaluate the efficacy of blue-light shield eyewear and blue-light cut LEDs on glucose and lipid metabolism, as well as anthropometric data. We have previously reported that blue-light shield eyewear was beneficial in...
protecting against retinal damage, reducing eye fatigue, relieving dry eyes, and improving sleep quality. The eyewear used in this study more strongly reduces blue light than those we used previously. Furthermore, in the animal experiments using a light-pulse model, we evaluated molecular mechanisms underlying blue-light effects on glucose and lipid metabolism together with the effects on circadian rhythms.

**MATERIALS AND METHODS**

**Experiment 1: Animal Studies**

**Animals.** Six-week-old male C57BL/6j mice (Japan SLC, Hamamatsu, Japan) were used for all animal experiments. Animals were group housed with 12 hours of light and 12 hours of darkness (lights on at 8:00 AM, lights off at 8:00 PM; lights-off was defined as Zeitgeber time [ZT] 12; light intensity of 100–300 lux at the bottom of cage), with entraining to the light-dark (LD) cycle for at least 2 weeks. Food and water were available ad libitum.

All animal experiments were conducted in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research, and were approved by Keio University School of Medicine, Tokyo, Japan.

**Light Pulses.** For the light pulses, we used white LEDs with or without a blue-light cut shield (Jins, Inc., Tokyo, Japan) and blue-light cut LEDs (Toshiba Materials Co., Ltd., Yokohama, Japan) in a cage designed for light exposure (Mayo Corporation, Aichi, Japan). For all light-pulse experiments, animals were exposed to 10-lux light for 30 minutes at ZT 14.

**Phase Shift in Locomotor Activity Rhythm.** The mice were separated into two groups: the white LED group (n = 7) and blue-light cut group (n = 8). Each mouse was transferred to a cage of 150 mm (width) × 300 mm (length) × 150 mm (height), with a running wheel (100 mm in diameter) in a light-tight photoperiod box (equipped with a fan and timer-controlled light) with a 12:12-hour LD cycle (lights-on at 8:00 AM). Locomotor activity was measured as running wheel revolutions recorded in 1-minute bins by The Chronobiology Kit (Stanford Software Systems, Santa Cruz, CA, USA).

After a week of recording, the mice were exposed to a 10-lux light pulse (white LED or blue-light cut light) for 30 minutes at ZT 14 and subsequently transferred into constant darkness (dark control) for 2 weeks. Phase shifts were determined by measuring phase differences between eye-fitted lines connecting the onsets of activity for 7 days before and 14 days after the light pulse.

**SCN Tissue Collection After Light Pulse.** The mice were separated into three groups: dark control (n = 5), white LED group (n = 5), and blue-light cut group (n = 5). They were group housed in a light-tight photoperiod box with a 12:12-hour LD cycle. After a week of habituation, the mice were exposed to a 10-lux light pulse for 30 minutes at ZT 14 and euthanized by cervical dislocation at ZT 17 and 20. The brain was removed, placed in chilled PBS, and sliced in the coronal plane on a vibratome (Dosaka EM, Kyoto, Japan) at a thickness of 500 μm. Using a stereoscopic microscope, we isolated the bilateral SCN, and a minimum of surrounding tissue was used. Then, the tissue was placed in chilled PBS, and sliced in the coronal plane on a vibratome (Dosaka EM, Kyoto, Japan) until later use.

**Assessing Metabolism.** Animals were fed with a high-fat diet (High fat diet 32; CLEA Japan, Inc., Tokyo, Japan) for 1 week under a 12:12-hour LD cycle. Subsequently, animals were exposed to the light pulse. We analyzed blood sugar levels with a glucometer (TERUMO, Tokyo, Japan) 24 and 48 hours after the light pulse. Samples from the liver and quadriceps femoris muscle were collected 48 hours after the light pulse.

**Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR).** Total RNA was isolated from the SCN, liver, and quadriceps femoris muscle after exposure to the light pulse and then reverse-transcribed. Quantitative PCR analyses for Per2, ATP-binding cassette transporter A1 (Abca1), ATP-binding cassette transporter G1 (Abcg1), cyc36, heme oxygenase (Hmox1), superoxide dismutase (Sod1), sterol regulatory element-binding protein (Srebp1a), insulin receptor substrate (Ir1), ldr2, and glyceroldehyde-3-phosphate dehydrogenase (Gapdh) were performed with a StepOnePlus Real-Time PCR System (Applied Biosystems, Foster City, CA, USA) in combination with TaqMan probes (Applied Biosystems). The level of each mRNA was normalized to that of Gapdh.

**Experiment 2: Clinical Study**

**Participants.** Participants were recruited via an advertisement at an eye hospital and pharmacy in a large medical group. Inclusion criteria were regular habitual sleep, normal vision, no sleep medicine, and good general health according to a workplace health check. Normal vision was confirmed by an ophthalmologist for all participants before they completed the study. Exclusion criteria were history of shift work, overseas travel in the previous 6 months, use of sleep medication, and any history of psychiatric illness. Participants maintained their usual weekday lifestyle before the study period. This study was conducted in accordance with the tenets of the 1995 Declaration of Helsinki.

The study was conducted from January to February 2016 in Akita, Japan, where the latitude is 39.26°N and day length varies by 4 to 6 hours over the year according to averages for 1981 through 2010 reported by the Japan Meteorological Agency.

The clinical study (registered through the University hospital Medical Information Network [UMIN] Center, number UMIN000021158, registered on February 24, 2016) was approved by the Institutional Review Board of Shinseikai Toyama Hospital, Imizu, Japan. All participants provided written informed consent.

**Study Design.** For 1 month, participants were asked to live their daily life while wearing blue-light shield eyewear for 2 to 3 hours before bed.

**Light Transmittance of Eyewear.** The experimental blue-light shield eyewear worn by participants in this study was brown-tinted and designed to transmit 0.0% of visible blue light (395–490 nm) and 30.0% of whole luminous light. These specifications were measured according to the International Organization for Standardization manual regarding sunglasses and related eyewear (https://www.iso.org/standard/51351.html). Participants wore the experimental eyewear without any other form of eyewear.

**Anthropometric Data and Laboratory Tests.** We measured participants’ age, sex, systolic and diastolic blood pressure (mm Hg), body weight (kg), height (cm), calculated body mass index (kg/m²), and waist circumference (cm). Laboratory measurements were collected, including fasting plasma glucose (FPG; mg/dL), plasma insulin (U/mL), C-peptide (ng/mL), high-density lipoprotein cholesterol (HDL-ch; mg/dL), low-density lipoprotein cholesterol (LDL-ch; mg/dL), triglyceride (TG; mg/dL), aspartate transaminase (AST; U/L), and alanine aminotransferase (ALT; U/L). To quantify insulin resistance and β-cell function, we calculated the homeostasis model assessment of β-cell function (HOMA-β) and homeostasis model assessment of insulin resistance (HOMA-IR). HOMA-IR is an index designed to easily quantify insulin resistance and is extensively used. In general, if the fasting blood glucose level is about 130 to 140 mg/dL, HOMA-IR is...
considered to be a good indicator of insulin resistance. It can be calculated with the following formula: fasting insulin level (\(\muU/mL\)) × fasting blood glucose level (mg/dl) / 405.

HOMA-\(B\) is one of the indicators of insulin secretion function. It can be calculated with the following formula: HOMA-\(B\) = fasting insulin level (\(\muU/mL\) × 360) / fasting blood glucose level – 63 (mg/dl). Thirty (%) or less is considered to be a decrease in insulin secretion.

**Sleep Quality and Mood Status Questionnaires.** Before inclusion and 1 month after initiation of the experiment, participants completed validated questionnaires including the Pittsburgh Sleep Quality Index (PSQI)\(^{23}\) and the Center for Epidemiologic Studies Depression Scale (CES-D).\(^{24}\) PSQI comprises seven subscales and the CES-D comprises 20 questions. The cutoff for possible sleep disorder was a PSQI score of 5/6, and the cutoff for depression was a CES-D score of 15/16.

**Urine Melatonin.** First-morning-void urine samples were collected from all participants at baseline and 1 month after intervention initiation. The samples were frozen immediately and stored at \(-20^\circ C\) until testing was undertaken. Urinary 6-sulfatoxymelatonin levels were measured with an enzyme-linked immunosorbent assay (ELISA) using a Melatonin-Sulfate Urine ELISA kit (IBL International GmbH, Hamburg, Germany). The sensitivity of this assay was 0.41 ng/mL, and the intra- and interassay coefficients of variation were 1.2% and 5.7%, respectively. To adjust for variation in the dilution of urine, the 6-sulfatoxymelatonin concentration was expressed as urine 6-sulfatoxymelatonin/urine creatinine with the LabAssay Creatinine (Jaffe method) (Wako Pure Chemical Industries, Ltd., Tokyo, Japan).

**Statistical Analyses.** All results are expressed as the mean ± standard error (SE). Commercially available software (SPSS version 23.0, IBM Corporation, Armonk, NY, USA) was used for statistical analysis; \(P < 0.05\) was considered to be statistically significant. One-way ANOVA post hoc tests and paired \(t\)-tests were used to assess the statistical significance of differences.

**Data Availability.** The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**RESULTS**

**Experiment 1: Animal Studies**

**Phase Shift After White and Blue-Light Cut Light Pulse.** Mice were maintained under a 12:12-hour LD cycle for 1 week before being exposed to 10-lux light for 30 minutes with a white LED or blue-light cut LED at ZT 14 (Fig. 1A). Spectrums of white and blue-cut LED lighting used in the experiment are shown in Figure 1B. For 2 weeks after the light pulse, we recorded a raster scan for wheel running in mice exposed to a 30-minute light pulse with white (Fig. 1C) or blue-light cut LED (Fig. 1D). We observed that the phase shift with blue-light cut light pulses was significantly higher than that with white light pulses (44.7 ± 11.9 vs. 107.7 ± 9.9 minutes, respectively; Fig. 1E). The \(Per2\) expression in the SCN at 3 hours after white light pulses was significantly higher than after dark or blue-cut light pulses (Fig. 2).

**Blue-Light Cut Light Pulse Improves \(Irs2\) Expression Levels in the Liver and Muscle.** We observed significantly lower blood glucose levels 48 hours after blue-cut light cut light pulses than after white light pulses (Fig. 3). Subsequently, we examined the effects of blue-light cut light on insulin-signaling pathways in the liver with quantitative polymerase chain reaction (PCR). The decrease in \(Irs2\) expression induced by a white light pulse was significantly recovered with a blue-cut light pulse (Fig. 4A). In contrast, there were no marked differences in \(Irs1\) and \(Glut4\) mRNA expression in the murine liver among the dark, white light pulse, and blue-light cut light pulse conditions (Figs. 4B, 4C).

\(Abcg1\) plays a critical role in mediating cholesterol efflux to high-density lipoprotein (HDL) and preventing cellular lipid accumulation. We observed that \(Abcg1\) expression induced by a white light pulse was suppressed by a blue-cut light pulse (Fig. 4E). In the skeletal muscle, \(Irs2\) expression was significantly increased following a blue-cut light pulse (Fig. 5).
5A). There were no significant differences in Abcg1 and Srebp1a expression in the skeletal muscle between white light pulses and blue-light cut light pulses (Figs. 5D, 5E).

Experiment 2: Clinical Study

Anthropometric Data. Six healthy Japanese adults (age range, 30–56 years; mean age, 41.7 ± 6.8 years; male/female, 3/3) participated in the clinical trial. Figure 6A shows the blue-light shield eyewear worn by participants for 2 to 3 hours before bedtime for 1 month. There were no changes in anthropometric data between baseline and 1 month after intervention initiation. Mean values at baseline and after 1 month were 61.3 ± 4.9 and 61.2 ± 4.7 kg (P = 0.880, paired t-test) for body weight, 22.5 ± 0.9 and 22.2 ± 0.9 kg/m² (P = 0.693) for calculated body mass index, 81.7 ± 2.7 and 82.0 ± 2.4 cm (P = 0.465) for waist circumference, 119.0 ± 5.1 and 119.2 ± 5.3 mm Hg (P = 0.926) for systolic blood pressure, and 74.2 ± 6.6 and 68.2 ± 3.9 mm Hg (P = 0.086) for diastolic blood pressure, respectively (Table).

Laboratory Data. After 1 month of wearing blue-light shield eyeglasses, there were significant reductions in FPG and HOMA-IR, indicating amelioration of insulin resistance (Fig. 6; Table). There was a significant increase in AST but there were no significant effects on other parameters.

The mean values at baseline and after 1 month were 84.8 ± 4.2 and 81.5 ± 4.0 mg/dL (P = 0.030, paired t-test) for FPG (Fig. 6B), 7.05 ± 1.91 and 5.28 ± 1.52 U/mL (P = 0.056) for plasma insulin (Fig. 6C), 1.57 ± 0.29 and 1.40 ± 0.22 ng/mL (P = 0.578) for C peptide (Fig. 6D), 124.2 ± 28.5 and 101.3 ± 17.6 mg/dL (P = 0.113) for TG (Fig. 6G), 71.3 ± 9.6 and 72.5 ± 10.3 mg/dL (P = 0.728) for HDL-ch (Fig. 6H), 131.3 ± 7.1 and 138.7 ± 10.4 mg/dL (P = 0.401) for LDL-ch (Fig. 6I), 30.2 ± 5.4 and 30.8 ± 6.3 U/L (P = 0.781) for ALT (Fig. 6J), 20.8 ± 1.8 and 23.8 ± 2.7 U/L (P = 0.030) for AST (Fig. 6K), 131.4 ± 41.7 and 107.7 ± 24.2 (P = 0.449) for HOMA-β (Fig. 6E), and 1.51 ± 0.42 and 1.13 ± 0.38 (P = 0.032) for HOMA-IR (Fig. 6F), respectively.

Sleep Quality and Depression Status. The mean PSQI global score was 5.50 ± 0.61 at baseline and 3.83 ± 0.28 after
1 month ($P = 0.030$, paired t-test; Fig. 6L; Table). Furthermore, the mean sleep duration (hours) was 5.67 ± 0.22 and 5.92 ± 0.22 ($P = 0.271$), while sleep efficacy (%) was 88.6 ± 3.5 and 94.0 ± 2.6 ($P = 0.165$) at baseline and after 1 month, respectively. The overnight urine 6-sulfatoxymelatonin concentration was 23.6 ± 5.2 ng/mL at baseline and 24.0 ± 7.0 ng/mL after 1 month ($P = 0.467$). Participants had a mean CES-D score of 14.7 ± 1.3 at baseline and 14.8 ± 1.9 after 1 month ($P = 0.894$; Fig. 6M).

**DISCUSSION**

In this study, we demonstrated that blue light disturbs circadian rhythms by interfering with the clock gene in the SCN. Meanwhile, suppression of blue light at night improves metabolic abnormalities by controlling circadian rhythms.

Blue light is visible light ranging from 400 to 500 nm in wavelength and plays pivotal roles in stimulating intrinsically photosensitive retinal ganglion cells (ipRGCs) to maintain systemic homeostasis and maintains and resets circadian rhythms. In the animal experiment, phase shift induced by blue-cut light pulses was significantly shorter than that induced by white light pulses (Fig. 1E). Additionally, there were significant differences in the expression of the clock gene, *Per2*, in the SCN between white and blue-cut light pulses (Fig. 2). These results indicate that blue light disturbs circadian rhythms by interfering with clock genes in the SCN.

Moreover, the clinical study demonstrated that blue-light shield eyewear improved subjective sleep quality, which in turn likely contributes to metabolic improvements (Fig. 6). Here, we measured both sleep quality and depression status because they are closely related to each other. Our results suggested that improvements in sleep following use of blue-light shield eyewear was not associated with depressive mood. We have previously reported that blue-light shield eyewear improves sleep efficacy and sleep latency measured with an actogram and that blue light induces circadian rhythm disorder. Blue-light shield eyewear offers an inexpensive, safe, and easy method of controlling exposure to blue light.

Both our experimental and clinical results demonstrate the potential effects of blue light on glucose metabolism and liver function. Blood glucose levels 48 hours after a blue-light cut light pulse were significantly lower than those after a white light pulse (Fig. 3), and blood glucose levels were significantly lower after using blue-light cut eyewear (Fig. 6). The liver plays an important role in glucose and lipid metabolism. Insulin suppresses gluconeogenesis and increases fat synthesis in the liver,25 as well as increasing glucose transport to muscle to decrease blood glucose. In the insulin resistance of obesity, insulin-stimulated glucose transport and metabolism is decreased in adipocytes and skeletal muscle, while suppression of hepatic glucose output occurs.26

Insulin IRS1 and IRS2, highly expressed in the liver, are cytoplasmic signaling molecules that mediate the effects of insulin by acting as molecular adaptors between diverse receptor tyrosine kinases and downstream effectors.25,27 *Irs1*−/- mice show growth retardation and are insulin-resistant, but do not develop diabetes because IRS2 compensates for the lack of IRS1 in the liver.28,29 In contrast, mice lacking systemic IRS2 develop diabetes due to insulin resistance in the liver and β-cells.30 Therefore, IRS2 is a molecule that plays a major role in the regulation of insulin signaling in the liver.28,31 In the

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**FIGURE 5.** Expression of glucose and lipid metabolism parameters in skeletal muscle after white and blue-light cut light pulses. Expression of *Irs2* (A) and *Glut4* (C) was significantly increased after blue-cut light pulses. There were no marked differences in *Irs1* (B), *Sreb1a* (D), and *Abcg1* (E) expression among the dark, white light pulse, and blue-light cut light pulse conditions. *P < 0.05.
FIGURE 6. Clinical parameters after wearing blue-light shield glasses at night. Blue-light shield eyewear is shown in (A). Glucose metabolism including fasting plasma glucose (B), fasting insulin (C), and C peptide (D) before and after 1-month use of blue-light shield eyewear at night was measured. Fasting plasma glucose decreased significantly. HOMA-β (E) and HOMA-IR (F) before and after 1-month use of blue-light shield eyewear at night were also measured, with HOMA-IR showing significant decreases. Lipid metabolism including triglyceride (G), HDL-ch (H), and LDL-ch (I) levels before and after 1-month use of blue-light shield eyewear at night are shown. Liver function including ALT (J) and AST (K) before and after 1-month use of blue-light shield eyewear at night was observed, with significant increases in AST. Subjective sleep quality (assessed with PSQI) (L) and depression (assessed with CES-D) (M) were assessed before and after 1-month use of blue-light shield eyewear at night. There were significant improvements in PSQI. *P < 0.05, paired t-test.
context of liver insulin resistance, transcription of IRS2 is sustained.32

The HOMA-IR is frequently used as an indicator of insulin resistance.35 In our clinical study, HOMA-R showed significant improvements, with significantly decreased blood glucose after the use of blue-light shield eyewear (Fig. 6). Additionally, transcription of IRS2 was suppressed by white light but showed a significant increase following a blue-light cut light pulse in the animal model (Fig. 4). In a previous study, circadian disruption activated constitutive androstane receptor (CAR) by promoting cholestasis, peripheral clock disruption, and, sympathetically dysfunction.34 Moreover, time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet.35 These results indicate the importance of circadian rhythms for liver and metabolic disorders. Collectively, they suggest that blue light induces insulin resistance by suppressing IRS2, an important molecule in insulin signaling in the liver, by altering circadian rhythms.

High lipid consumption causes accumulation of lipid in the liver and disrupts insulin signaling, resulting in insulin resistance.36 ABCG1 is critical for mediating cholesterol efflux to HDL and preventing cellular lipid accumulation.37 In our study, ABCG1 expression induced by white light pulses was suppressed by blue-cut light pulses. Lipid accumulation due to ABCG1 downregulation is a possible mechanism of insulin resistance in the liver. GLUT4 is the insulin-regulated glucose transporter found in skeletal muscle and adipose tissue.38 Activation of GLUT4 increases transport of blood glucose to skeletal muscle and adipose tissue to reduce blood levels of glucose. GLUT4 upregulation in skeletal muscle and IRS2 upregulation in the liver are mechanisms by which blue light may reduce blood glucose.

This study is limited by the small sample size and short study period. Moreover, future studies should assess sleep quality with polysomnography. Nonetheless, our results suggest a potentially important role of blue light in sleep and metabolism, which can be reversed with interventions to protect from blue light.

In summary, blue light appears to disturb circadian rhythms by interfering with clock genes in the SCN. Conversely, suppression of blue light at night improves metabolic abnormalities by controlling circadian rhythms. A more detailed understanding of the underlying mechanisms could aid the future development of new therapies aimed at preventing blue-light exposure resulting in metabolic impairments.

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References

TABLE Clinical Parameters After Wearing Blue-Light Shield Glasses at Night

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<th>Parameters</th>
<th>Baseline</th>
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<td>81.5 ± 4.0</td>
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<td>Plasma insulin, U/mL</td>
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<td>Triglyceride, mg/dL</td>
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<td>71.3 ± 23.5</td>
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<td>Sleep efficiency, %</td>
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<td>14.7 ± 1.3</td>
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Data are shown as mean ± SE.

* P < 0.05, paired t-test.


