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ARTICLE

Melatonin attenuates light-at-night effects on systolic blood pressure and body temperature but does not affect diastolic blood pressure and heart rate circadian rhythms

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ABSTRACT

Aim of the present study is to assess whether 1.5mg of exogenous melatonin provided under modified CR in constant light (~400 lx) is capable to mimic effects of dark phase. Forty-six young adults (YA), 17–24 years old of both genders were studied under amodified CR protocol for 26 h. Initially, participants were investigated under constant light (CR-LL) and 2 weeks later under the same conditions though 1.5mg melatonin (Melaxen) was given orally at 22:30. Systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate (HR) and body temperature (BT) were measured every 2 h. To verify the effect of constant light, formerly published results obtained under light-dark conditions (CR-LD) were reanalyzed.

Administration of 1.5 mg of exogenous melatonin modified the 24 h patterns of BT and SBP within short 3.5 h time window but did not influence DBP and HR. A short-term reduction of SBP and BT for 1.5–3.5 hours was observed. The values in the CR-LL+M group were significantly lower than in CR-LL at 2:00 h. Hence, exogenous melatonin did mimic the scotophase. Though this effect was gender-specific and found only in female YA.

Results of this study prompt further research to qualify and quantify dosage-, duration- and time-dependent differences of melatonin effects, to discern between short-term (acute) and long-term (chronic) melatonin administration, and to clarify its underlying mechanisms.

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Melatonin; circadian rhythms; body temperature; blood pressure; heart rate; constant routine; ambient light; light at night; young adults; sex; gender

Introduction

Regular and predictable external cycles justify evolutionary emergence of the built-in genetic clocks (Bhadra et al. 2017). Hence, biological rhythmicity is a fundamental property of living beings that constitute multi-oscillatory systems (Aschoff 1965, Pittendrigh 1993, Bell-Pedersen et al. 2005, Laje et al. 2018). Circadian rhythms, in particular, are a ubiquitous feature of the single cell, though need to be synchronized

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and orchestrated both internally, with each other; and externally, with environmental time cues (Reppert and Weaver 2002, Merrow et al. 2005, Lamont et al. 2007, Golombek and Rosenstein 2010, Gubin 2013).

The light-dark cycle is the main zeitgeber, which entrains the endogenous rhythms to the 24-h environment. The non-image forming photic information is perceived by a subpopulation of retinal ganglion cells, the so-called intrinsically photosensitive retinal ganglion cells (ipRGC). The axons of these neurons form the retinohypothalamic tract (RHT), the main afferent pathway to the site of the central circadian clock, the paired suprachiasmatic nuclei (SCN) which are located in the hypothalamus (Weaver 1998, Freedman et al. 1999, Golombek and Rosenstein 2010, Markwell et al. 2010). Human SCN is tiny clusters of approximately 100,000 neurons, that orchestrates myriads of downstream functions in a rhythmic fashion (Bollinger and Schibler 2014). Nocturnal pineal hormone melatonin assists SCN providing signaling to the peripheral cells and back to SCN. Loss of integrity between rhythms either intrinsically within the body or extrinsically with external time cues provoke so-called circadian disruption that is potentially harmful for health and may cause certain pathologies (Karatsoreos et al. 2011, Salgado-Delgado et al. 2011, Gubin et al. 2013, Touitou et al. 2016).

Light is not only synchronizer but, if wrongly timed, it is a major factor for circadian disruption (c.f. (Gubin et al. 2017). Artificial light at night (ALAN) disrupts the biological clock and predisposes subjects toward the development of numerous diseases (c.f. (Anisimov et al. 2012, Fonken et al. 2013, Smolensky et al. 2015, Lunn et al. 2017). The light-induced reduction of melatonin production is largely responsible for these deleterious effects of ALAN (Anisimov et al. 2012, Bonmati-Carrion et al. 2014, Touitou et al. 2017). Nocturnal pineal hormone melatonin is an important internal cue transferring rhythmic signals to peripheral cells and back to the SCN. Furthermore, melatonin exerts numerous direct effects on physiologic functions including thermoregulation and sleep (Krauchi et al. 2006), and the cardiovascular system (Sun et al. 2016, Borghi and Cicero 2017, Favero et al. 2017) thus strengthen their circadian rhythms (Gubin et al. 2006, 2016a).

Specific response of cardiovascular variables to melatonin administration and its suppression by light may derive from either central or peripheral mechanisms, as both heart and vessels possess peripheral clocks that are modulated by the central clock and photic signaling (Curtis et al. 2004, Paschos and FitzGerald 2010, Martino and Young 2015, Chellappa et al. 2017a, 2017b). Besides, melatonin may exert its physiologic and circadian effects receptor-dependently or receptor-independently either via central mechanisms or by acting directly at peripheral cells (Reiter et al. 2014).

The effect of melatonin on cardiovascular functions and body temperature varies depending on dosage, timing and type of release (slow vs. controlled), but also age, gender and initial blood pressure (Scheer et al. 2004, Cagnacci et al. 2005, Grossman et al. 2006, Gubin et al. 2006, 2016a), particularly its nocturnal value, are crucial (Mozdzan et al. 2014). Also, acute (short-term) effects of a single administration may be different from those of long-term (chronic) administration (Scheer et al. 2004). We have shown that, melatonin application once per day over two weeks does strengthen the circadian body temperature (BT) and blood pressure (BP) rhythms in elderly persons (Gubin et al. 2006, 2016a). Moreover, a hypotensive effect was observed which was more pronounced the higher the blood pressure was before the treatment.

In a former study, we demonstrated that ambient light at night has a different and specific impact on circadian BP, heart rate (HR) and BT rhythms (Gubin et al. 2017). The evening drop of systolic BP and BT was delayed, especially in female subjects. A minor effect was observed for the diastolic BP and none for HR. We hypothesized that at least some of these effects were caused by a light-induced reduction of melatonin production. The aim of the present paper was to prove this hypothesis.

We investigated the acute effect of melatonin (half-tablet of Melaxen, 1.5 mg; Unipharm Inc., USA) administered at 22:30 upon the endogenous rhythms of BT, SBP, DBP and HR in normotensive young adults under our modified CR protocol in constant light (c.f. (Gubin et al. 2017). Melatonin dosing was kept similar to that of our previous works as it was shown to have prominent effect on temperature and blood pressure with repeated administration (Gubin et al. 2006, 2013, 2016a, 2016b); furthermore dosages even less than 1.5 mg were shown to have physiologic effects, sometimes being even more effective than higher dosages (Lewy et al. 2002). This approach also allowed checking whether a single melatonin dose is capable to mimic the effect of darkness. As reference, data from our previous study (Gubin et al. 2017) obtained also under constant routine conditions though with a normal LD cycle (CR-LD) were redrawn.

Material and methods

A total of 46 normotensive young adults (YA, aged 17–24 of both genders were studied under a modified CR protocol (Gubin et al. 2017) during several sessions in consecutive years though always in December and from Saturday to Sunday. Our modification of the original CR protocol allows low activity (standing, making a few steps) but no sleep. The team of observers (2 young researchers for each room, who replaced each other every 4 h) did help the participants to stay awake. Within 60 min before each measurement, the participants had to be seated but could talk, listen to music or read (if there were lights on). Meals were equally distributed at small portions throughout the day. After each measurement, small similar meals (~215 kcal) were provided. The content of proteins, carbohydrates and lipids were similar – 30 ± 5; 50 ± 10, and 20 ± 5%, respectively.

Each experimental session lasted for 26 h. Systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR) and body temperature (BT) were measured every 2 h, beginning at 12:00, i.e. after 2 h of pre-adaptation to experimental conditions. For each individual, measurements were made using the same mercury thermometer or the same A&D BP monitor with manual cuff inflation.

Forty-six young adults (34 females, 12 males) were engaged in two consecutive sessions (CR-LL and CR-LL+M) performed 2-weeks apart:

- **CR-LL** Lights were on (~400 lx) during the whole experimental session.
- **CR-LL+M**: Lights were on (~400 lx) during the whole experimental session. 1.5 mg melatonin (Melaxen) was administered orally at 22:30, i.e. 30´ before the average bedtime.

Previously published data (Gubin et al. 2017) obtained also under modified constant routine but with a light-dark cycle were used as a reference. Except for lighting

conditions, the experimental design was the same as in the present study. Also, due to considerable sample sizes, putative inter-individual differences will fade, what makes it possible to use the data of this different group as reference.

- **CR-LD** (n = 77; 53 females, 24 males): The light-dark (LD) regimen was similar to that of local photoperiodic environment in December at 55° north latitude. Accordingly, lights were on (~400 lx) from session start at 12:00 until 17:00 and from 09:00 on the second day and were off (<10 lx) from 17:00 to 09:00 next morning.

Medical University students and staff members are required to undergo a medical examination upon admission. Considering these data, all participants of CR and control groups were presumably normotensive according to current guidelines (Mancia et al. 2013).

All participants were university students with regular everyday life and no additional physical activity (i.e. no workouts). They had similar sleep-wake schedules gauged by a personal diary: activity phase between 06:00–07:00 (no later than 08:00 at weekends) and 22:00–00:00 and 3 meals per day during the week preceding the CR sessions. Male and female participants were not different in average body mass within CR-LL (CR-LL+M) group ($p = .443$), and CR-LD groups ($p = .205$); there were also no difference for mean body mass between the groups ($p = .318$). None of the participants were engaged in shift or night work during the week preceding data collection. Also, no chronic endocrine or nutritional/metabolic disorders, diseases of eyes, of the central nervous, the circulatory or the respiratory systems had been diagnosed.

Data are always presented as mean values with standard errors. ANOVA and tests on statistical significance were performed using the software package Excel and SPSS 12.0. Shapiro-Wilk's W-test was applied to check for normal distribution. The level of statistical significance was set at $p < 0.05$. For further details and exact p-values see Results section.

Circadian rhythm parameters (amplitude and acrophase) of the raw data and of the data expressed as percentage of individual mean values were estimated by single Cosinor analysis (Cornelissen 2014). The group-mean values were compared by Bingham's parameter tests (Bingham et al. 1982).

Results

Twenty-four-hour patterns of BT, BP and HR under the three different CR regimens (CR-LL; CR-LL+M and CR-LD) are shown in Figure 1. Results comparing continuous light at night (CR-LL) and regular light-dark conditions (CR-LD) were described already elsewhere (Gubin et al. 2017). Similar results were found in the present study. Constant light of ~ 400 lx delayed the evening decrease of BT by about 2 h – from 22:00 to 00:00 h. SBP increased in the CR-LL group both in the former dark and the former light phases. The effect on DBP was less pronounced. No significant differences were found for HR between CR-LL and CR-LD.

BT circadian rhythms were similar under CR-LL and CR-LL+M regimen (Figure 1), except for the first hours after melatonin application. The BT decrease was steeper in the CR-LL+M group. At 02:00 h, BT tended to be lower ($p = 0.07$) than in CR-LL, though it was equal to the value in CR-LD. This indicates that melatonin may have accounted for

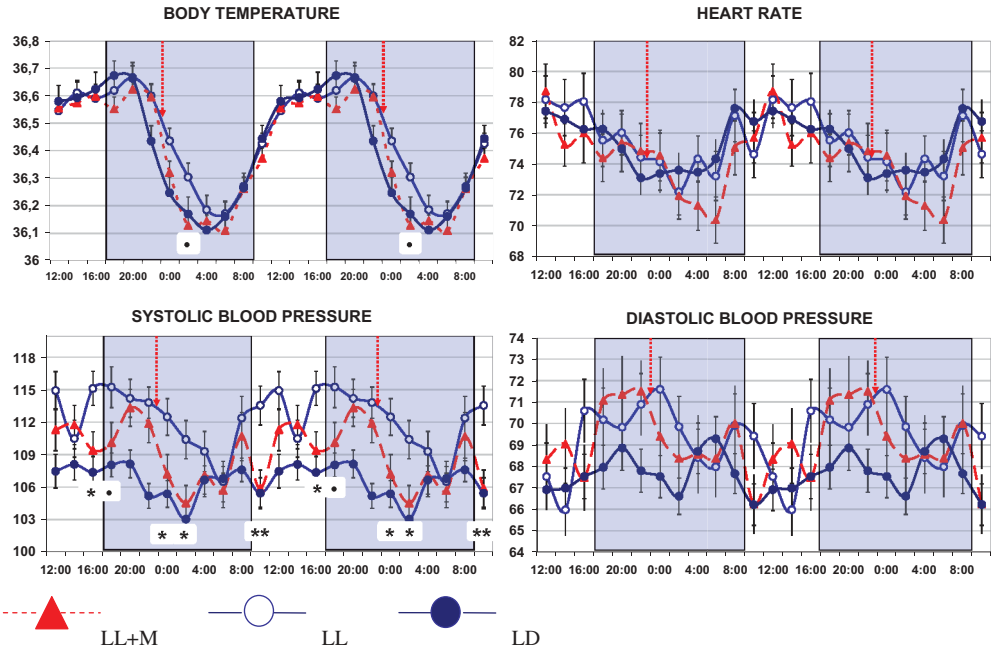

Figure 1. Effect of ambient light and melatonin on body temperature, systolic/diastolic blood pressure and heart rate in normotensive young adults assessed under constant routine protocol.

Circadian profiles obtained under constant light of ~400 lx (CR-LL); under constant light of ~400 lx with 1.5 mg melatonin administered at 22:30 (CR-LL+M) and under lighting conditions corresponding to the natural light/dark cycle (CR-LD, redrawn from Gubin et al. 2017). The 2nd 24-h cycle is an exact replication of the 1st and shown for better visualization. Shaded area: dark phase (<10 lx) of the CR-LD group.Red dotted vertical lines indicate timing of melatonin administration.CR-LL, n = 46; CD-LL+M, n = 46; CR-LD, n = 77.Significant differences between corresponding 2-hour mean values of CR-LL and CR-LL+M groups (paired t-test):*p < 0.05; **p < 0.01; ● borderline, p < 0.1.

the lower BT at this time. Maximum BT lowering effect of melatonin occurred at 02:00, i.e. approximately 3.5 h after its administration at 22:30. For SBP also, a steeper decrease was observed after melatonin administration (Figure 1). The SBP values at 0:00 and 2:00 h were lower in CR-LL+M than in CR-LL but similar as in CR-LD, indicating an acute melatonin effect on SBP within 3.5 h after its administration at 22:30. Neither for DBP nor for HR, significant differences between three CR regimens were found and particularly during the habitual nocturnal phase. As in our former study (Gubin et al. 2017), the effects of light on BT and BP were gender-specific with more prominent response in female young adults. Likewise, significant melatonin effects on BT and SBP were found only in female subjects, Figure 2.

Results of COSINOR analyses of cardiovascular variables are shown in Table 1. Since, there was no significant effect of melatonin administration on DBP and HR, and the effect on SBP was limited to the narrow time window (00:00–02:00 H), daily patterns and circadian rhythm parameters of the two consecutive series are highly consistent and reproducible. A direct effect of melatonin on MESOR, amplitude, and acrophase was absent, i.e. no significant differences between CR-LL and CR-LL+M were found. Noteworthy, an evening position of circadian acrophase was confirmed for all parameters in both time-series. However, the acrophases of SBP, DBP and HR are all significantly different from each other. DBP has the latest phase that differs from both

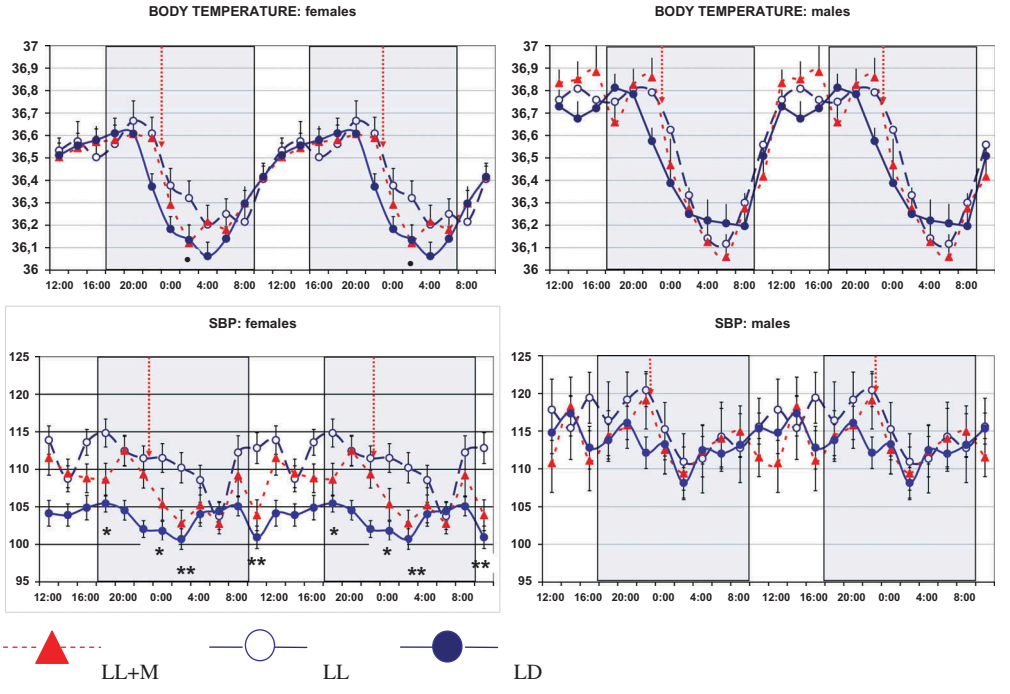

Figure 2. Gender-dependent effects of melatonin on body temperature and systolic blood pressure (SBP).

Circadian profiles obtained under constant light of ~400 lx (CR-LL); under constant light of ~400 lx with 1.5 mg melatonin administered at 22:30 (CR-LL+M) and under lighting conditions corresponding to the natural light/dark cycle (CR-LD) are depicted.CR- LL and CR-LL+M: data from the same individuals, who participated in both sessions, performed 2 weeks apart (34 women and 12 men); CR-LD: 53 women and 24 men (reanalyzed data from Gubin et al. 2017).The 2nd 24-h cycle is an exact replication of the 1st and shown for better visualization. Shaded area: dark phase (<10 lx) of the CR-LD group.Red dotted vertical lines: timing of melatonin administration.In female young adults, BT and SBP declined after melatonin application until 02:00 when BT and SBP became similar to values obtained under LD conditions but lower than in LL. Similar changes were found in male young adults, though differences were statistically not significant.Significant differences between corresponding 2-h mean values of CR-LL and CR-LL+M groups (paired t-test): *p < 0.05; **p < 0.01; ● borderline, p < 0.1.

SBP ($p \leq 003$) and HR ($p < .0001$) and peaking at approximately 22:30. SBP and HR mid-phase positions are also different ($p = 0.049$), SBP acrophase falls at 17:00, and HR has the earliest acrophase at about 14:00.

Results of ANOVA for the effects of group (CR-LL vs. CR-LL+M), time of day and gender are shown in Table 2. A significant effect of group was found for SBP, an effect of gender for BT, SBP and DBP. Significant interactions were obtained for BT (time*gender) and for DBP (group*gender). A significant time of day effect was found for all functions except DBP. This is mainly due to the substantial inter-individual variability. Expressing each value as the percentage of the individual mean allows validating a significant DBP circadian rhythm with nocturnal acrophase, Table 1.

Discussion

In an earlier study (Gubin et al. 2017), we have shown that ambient light of ~400 lx affects BP and BT in constant routine (CR-LL) depending on the time of the day and gender. The decline of BT and BP during the hours corresponding to the former dark

Table 1. Cardiovascular (systolic blood pressure: SBP; diastolic blood pressure: DBP; heart rate: HR) circadian rhythm parameters in constant routine under continuous light (CR-LL) and under continuous light with melatonin at 22:30 (CR-LL+M). Data of 46 subjects (34 women, 12 men) expressed as percentage of individual daily means were analyzed. Mean values and standard errors for individual estimates of 24-h PR, Amplitude and phase are indicated. Single melatonin dosing exerts no acute effect on circadian rhythm parameters under CR-LL (no significant differences between CR-LL vs. CR-LL+M). Time patterns and rhythm parameters from 2 consecutive series 2 weeks apart are highly consistent and reproducible, though melatonin administration increases DBP percentage rhythm.

	PR ± s.e. (p-value)		Amplitude ± s.e.		24 phi (95% CI)	
	CR-LL	CR-LL + M	CR-LL	CR-LL + M	CR-LL	CR-LL+M
SBP	25.61 ± 3.00 (<.001)	29.49 ± 3.17 (<.001)	7.12 ± 0.96	6.71 ± 1.00	−255 (−234; −277)	−252 (−231; −273)
DBP	22.50 ± 2.76 (.008)	**31.32 ± 3.10*** (.002)	5.77 ± 0.53	7.08 ± 0.58	−340 (−301; −19)	−318 (−285; −351)
HR	27.02 ± 2.44 (<.001)	31.61 ± 2.71 (<.001)	6.39 ± 0.56	7.12 ± 0.57	−210 (−189; −231)	−222 (−200; −243)

PR (percentage rhythm), amplitudes and phase position are from linear least-square approximation of a cosine curve with a 24-h period; mean values and corresponding standard errors, in the case of the 24-h rhythm phase position mean values and the 95%- confidence interval are shown. P-values indicate the probability of a 24-h rhythm (no rhythm Ho derived from populational cosinor-analysis); s.e. – standard error; *p < .05 for differences between LL and LL+M regimen.

Table 2. Effects of melatonin (group), time and gender on body temperature (BP); systolic (SBP), diastolic blood pressure (DBP) and heart rate (HR) in CR-LL. Results from ANOVA of constant routine protocol under constant light (CR-LL) vs. CR under constant light with 1.5 mg melatonin administered at 22:30 (CR-LL+M). Raw data from the same individuals (n = 46), who participated in the 2 consecutive sessions, 2 weeks apart; 34 women and 12 men).

	Group		Time of Day		Gender		Group*Time		Group*Gender		Time*Gender	
	F ratio	*p* value	F ratio	*P* value	F ratio	*p* value	F ratio	*p* value	F ratio	*p* value	F ratio	*p* value
BT	0.61	.437	**20.68**	**.000**	**21.32**	**.001**	0.44	.937	0.01	.906	**1.94**	**.031**
SBP	**12.49**	**.000**	**2.63**	**.003**	**43.15**	**.000**	0.84	.597	1.02	.312	0.89	.551
DBP	1.96	.161	1.22	.268	**12.03**	**.001**	0.71	.731	**12.45**	**.000**	0.58	.846
HR	0.19	.665	**2.24**	**.011**	2.15	.143	0.61	.826	*3.41*	*.065*	0.57	.858

Significant effects (p < 0.05) are in **bold**, borderline values (p < 0.1) in *italic*.

phase was reduced and, more prominently in female young adults. We hypothesized that such effects of ambient light were partially caused by suppression of endogenous melatonin production during the former habitual dark phase. Therefore, the present study was aimed to evaluate whether a single dose of exogenous melatonin administered under modified constant routing conditions (CR-LL) is capable to counterbalance the effects of ambient light during habitual scotophase.

The effects of light during the first hours of the former dark time were similar to those obtained in our earlier study (Gubin et al. 2017). Under conditions of constant routine and constant light (CR-LL) the evening decrease of BT and SBP was delayed especially in female subjects. A minor effect was found for DBP and none for HR. Other authors also could not document effect of blue light on HR while documenting the effect on BP (Silva-Urra et al. 2015, Wu et al. 2015). Silver-Urra an co-workers compared effects of natural light spectra with more narrow blue light (bLED) spectra of light intensity 30 lx under hypobaric conditions in young adults and ended up with the conclusion that blue light affected BP female-gender-specifically but had no effect on HR. Wu et al. tested direct effects of higher light intensities (10–24 mW/mm^2) on isolated smooth muscle cells and hearts of mice and showed that light caused intensity-dependent

vasoconstriction but did not affect HR. Though, the light of an intensity of 800 lx or higher was capable to impact adrenal function and HR (Jung et al. 2010, Chellappa et al. 2017a).

The main purpose of this study was to investigate whether a single melatonin application is able to mimic the effect of dusk on distinct physiologic variables. According to obtained results, it indeed exerts a short-term effect similar to that of scotophase (CR-LD pattern). However, the effect differed between variables and was significant only for BT and SBP. Also, the effect was present only in women, whose SBP and BT were reduced for 3.5 h after a single application of melatonin to values normally obtained under light-dark conditions. Though with respect to sex differences, we cannot exclude that the smaller number of male participants may have biased the outcome of the study. Possibility that individual estrous stages in females may have affected the obtained results cannot be excluded. It seems unlikely, however, as the large sample size would even out such effects.

The effects of acute melatonin administration mirrored the effects of constant light. The stronger the effects of light, the stronger were the effects of melatonin. Accordingly, a significant melatonin effect was found only for BT and SBP. As constant light had only a moderate effect on DBP and none on HR, also the effect of melatonin was moderate or absent accordingly. This is strong evidence in favor of our hypothesis that the effects of ambient light on BT and BP was mediated via melatonin suppression.

Among several exogenous factors (physical activity, sleep, feeding, and light) that mask the endogenous circadian, light is the principal one (Mrosovsky 1999, Weinert and Waterhouse 2007). Physical (wavelength, intensity) and temporal (timing, duration) properties of ambient light modulate circadian dynamics of the cardiovascular system, what may lead to the development of different pathologies (Paschos and FitzGerald 2010, Martino and Young 2015, Chellappa et al. 2017b). Just 1 h of light exposition at midnight with an intensity of 350 lx does suppress melatonin by 38% (McIntyre et al. 1989). Therefore, our LL regimen with a light intensity of 400 lx is expected to cause a similar suppression. Ambient, light affects circadian rhythms of body temperature (BT), heart rate (HR) and blood pressure (BP) differently, depending on application time and gender (Gubin et al. 2017).

It was reported that in women, pineal gland can be more sensitive when exposed to bright light at night (Monteleone et al. 1995) that may help to explain gender-related differences of the effect of light on BT and BP which were obtained in the present and in a former study (Gubin et al. 2017). Also, female gender may be predisposed for a stronger and/or a more immediate response of BP to endogenous nocturnal melatonin production (Gubin et al. 2017). Indeed, there are arguments that estrogens may modify or potentiate the cardiovascular effects of melatonin (Cagnacci et al. 2001, Tsuda 2006). Also at least, older women have significantly lower urinary melatonin excretion than older men independently of light exposure (Obayashi et al. 2015). In any case, women may have more benefits from melatonin administration.

Melatonin can affect both BP and HR also through other parts of the central nervous system, e.g. by improving compromised baroreflex modulation via area postrema (Girouard et al. 2004, Campos et al. 2013). In this case, beneficial modulator effects of melatonin may become evident mainly in circumstances of an already impaired cardiovascular function. Moreover, direct effects of melatonin on cardiovascular parameters

comprise receptor-specific and receptor-independent mechanisms as well as central and local pathways which may also depend on application time (Simko and Paulis 2007, Reiter and Tan 2009; Pechanova et al. 2014, Carranza-Madrigal et al. 2015). They may have a direct acute impact on BP through vascular diameter/tone and myocardial contractility/cardiac output (Paulis and Simko 2007, Pechanova et al. 2014). Receptor-mediated effects of melatonin are ambivalent: MT_1-cAMP-Ca^{2+} dependent smooth muscle cells vasoconstriction can be overwhelmed by MT_2/NO endothelium-dependent vasodilatation (reviewed in (Slominski et al. 2012, Pechanova et al. 2014). As MT1/MT2 receptor density varies in different tissues and depends on circadian time (Masana et al. 2000, Waly and Hallworth 2015), this may explain some of the time-dependent differences of melatonin impact on BP. Gender-related difference in MT-receptor density and (or) timing may also play its role. The antioxidative activity of melatonin is likely to be a part of its BP-lowering potential. It modifies the intracellular Ca^{2+}-calmodulin concentration (Pechanova et al. 2014) with effects reciprocal to that of MT-receptor-dependent mechanisms, i.e. relaxation and vasodilatation of smooth muscle cells and NO-synthase inhibition driven endothelium vasoconstriction.

Our present findings suggest that short-term (acute) effects of melatonin account only for a minor part of its hypotensive potential and not involve DBP. Also, there is no evidence for an acute effect of melatonin on HR. Yildiz and co-authors (Yildiz et al. 2006) reported similar results in their study on acute effects of oral melatonin administration on arterial extensibility: significant reduction of SBP, but not DBP and HR. On the other hand, Scheer and co-workers (Scheer et al. 2004) found no effect of single (acute) 2.5 mg melatonin administration on SBP/DBP in 16 men with untreated essential hypertension, but an effect became evident after 3 weeks. HR was not affected in both cases. According to Arangino and co-authors, melatonin in an even smaller dosage of 1 mg is capable to induce an acute reduction of catecholamines, i.e. noradrenalin (Arangino et al. 1999). As catecholamines more eagerly affect SBP rather than DBP (Vlachakis et al. 1977, Hoffstedt et al. 1996), this may help to explain the different acute responses to melatonin between SBP and DBP. Whereas, an acute effect of melatonin on vascular reactivity and catecholamine levels is evident both in women (Cagnacci et al. 1998) and men (Arangino et al. 1999), gender and timing-related differences of catecholamine and its response to melatonin likely exist (Silver 2018) (Cagnacci et al. 2000, Cappuccio et al. 2007). Furthermore, response to melatonin administration may dependent on individual initial conditions: e.g. melatonin acute effect on the artery pulsatility index is related to baseline values, being greater in men with higher baseline values (Cagnacci et al. 1998, Arangino et al. 1999).

As mentioned already, physiologic mechanisms and effects of acute vs. chronic melatonin administration may also be different (c.f. (Scheer et al. 2004). In our own former studies, melatonin attenuated age-related deteriorations of circadian rhythms. The rhythms of BP, HR and BT were resynchronized and in some cases even restored (Gubin et al. 2006, 2013, 2016a, 2016b). As melatonin was administered once daily for 2 weeks, this melatonin action may have been gained in the course of time and involved feedback effects on the central circadian oscillator, the SCN. In addition, melatonin is known to be effective for promoting healthy sleep and improving sleep quality (Ferracioli-Oda et al. 2013); and our recent data suggest that sleep is crucial for nocturnal decline of DBP and HR, rather than SBP (Gubin et al. 2017). As sleep was not allowed under CR, we were not able to assess sleep-dependent actions of melatonin, though it may enhance acute impact

of melatonin on BP and HR under real-life conditions. The present study describes acute effects a single melatonin dosing and thus helps to discern acute (short-term) from long-term effects on SBP, DBP, HR and BT. As the above-mentioned studies were performed on elderly subjects, individuals´ age must also be taken into account as another factor being causative for the different results.

Since maintaining nocturnal BP appears to be the primary task in treatment and prevention of hypertension (Hermida et al. 2017, Shurkevich et al. 2017), melatonin as a natural mediator of darkness owning chronobiotic, antioxidative, hypnotic and hypotensive properties looks highly appealing. However, scientific data concerning optimal timing, dosage and duration of exogenous melatonin administration ensuring best benefits is still lacking. Results of the present study show that even a single melatonin application may have beneficial effects. At the same time, further research is necessary to qualify and quantify dosage-duration-timing dependent differences of melatonin effects and to discern effects of short-term (acute) and long-term (chronic) melatonin administration, to uncover the underlying mechanisms. This also includes the measurement of melatonin blood concentrations. Moreover, experiments might be performed not only in December, when nights are longest and accordingly the melatonin maximum is most expanded but also in June when the dark time is shortest.

The results of the present study provide convincing evidence in favor of our hypothesis that physiologic effects of ALAN on BT, BP and HR are linked with suppression of melatonin. They also show that deleterious effects of light at night can be treated with exogenous melatonin.

Disclosure statement

No potential conflict of interest was reported by the authors.

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