ORIGINAL ARTICLE

Ethnic Differences in Nighttime Melatonin and Nighttime Blood Pressure: A Study in European Americans and African Americans

Jinhee Jeong,[1] Haidong Zhu,[1] Ryan A. Harris,[1] Yanbin Dong,[1] Shaoyong Su,[1] Martha S. Tingen,[1] Gaston Kapuku,[1] Jennifer S. Pollock,[2] David M. Pollock,[2] Gregory A. Harshfield,[1] and Xiaoling Wang[1]

BACKGROUND
Ethnic differences in nighttime blood pressure (BP) have long been documented with African Americans (AAs) having higher BP than European Americans (EAs). At present, lower nighttime melatonin, a key regulator of circadian rhythms, has been associated with higher nighttime BP levels in EAs. This study sought to test the hypothesis that AAs have lower nighttime melatonin secretion compared with EAs. We also determined if this ethnic difference in melatonin could partially explain the ethnic difference in nighttime BP.

METHODS
A total of 150 young adults (71 AA; 46% females; mean age: 27.7 years) enrolled in the Georgia Stress and Heart study provided an overnight urine sample for the measurement of 6-sulfatoxymelatonin, a major metabolite of melatonin. Urine melatonin excretion (UME) was calculated as the ratio between 6-sulfatoxymelatonin concentration and creatinine concentration. Twenty-four-hour ambulatory BP was assessed and nighttime systolic BP (SBP) was used as a major index of BP regulation.

RESULTS
After adjustment of age, sex, body mass index, and smoking, AAs had significantly lower UME ($P = 0.002$) and higher nighttime SBP than EAs ($P = 0.036$). Lower UME was significantly associated with higher nighttime SBP and this relationship did not depend on ethnicity. The ethnicity difference in nighttime SBP was significantly attenuated after adding UME into the model ($P = 0.163$).

CONCLUSION
This study is the first to document the ethnic difference in nighttime melatonin excretion, demonstrating that AAs have lower melatonin secretion compared with EAs. Furthermore, the ethnic difference in nighttime melatonin can partially account for the established ethnic difference in nighttime SBP.

Keywords: African Americans; blood pressure; ethnic difference; hypertension; melatonin; nighttime blood pressure.

doi:10.1093/ajh/hpz083

Blood pressure (BP) follows a diurnal pattern, characterized by a nocturnal fall and a morning rise. More importantly, abnormal diurnal BP patterns have significant implications for cardiovascular disease pathophysiology.[1,2] Particularly, increased nighttime BP predicts cardiovascular (CV) events and mortality better than an office visit BP or other ambulatory BP parameters, including daytime BP and 24-hour mean BP.[3–5]

Accumulating evidence suggests that the diurnal BP pattern varies by ethnicity. A higher nighttime BP and/or a blunted nocturnal decline in BP have been reported in African Americans (AAs) compared with Europeans Americans (EAs).[6,7] Our previous longitudinal study demonstrated that this ethnic difference can start as early as age 10.[8] Furthermore, this ethnic difference in nighttime BP has been linked to ethnic disparities in the prevalence of hypertension and its associated CV complications.[7] Thus, controlling nighttime BP is critical in reducing the disproportionally high CV morbidity and the associated mortality in AAs. However, the underlying etiology for this ethnic difference in nocturnal BP pattern is still poorly understood.

Melatonin is a hormone produced predominantly at night by the pineal gland and plays an important role in the regulation of biological circadian rhythms including BP regulation.[9,10] Melatonin is excreted in the urine as 6-sulfatoxymelatonin (aMT6s), and aMT6s is a well-established proxy measurement of circulating melatonin.[11,12] Abnormalities in melatonin secretion have been linked with the pathophysiology of hypertension and subsequent CV disease.[9,10,13] Low levels of overnight urine melatonin have been associated with higher nighttime BP or blunted nocturnal decline in BP in Caucasians and Asians.[10,13] However,

Correspondence: Xiaoling Wang (xwang@augusta.edu).

Initially submitted March 28, 2019; date of first revision April 26, 2019; accepted for publication May 20, 2019; online publication May 21, 2019.

[1]Department of Population Health Sciences, Georgia Prevention Institute, Medical College of Georgia, Augusta University, Augusta, Georgia, USA; [2]Cardio Renal Physiology and Medicine Section, Division of Nephrology, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA.

whether this is also the case in AAs and whether ethnic differences exist in endogenous melatonin secretion are currently unknown.

Considering that AAs exhibit higher nighttime BP, this study sought to test the hypothesis that AAs have lower nighttime melatonin secretion compared with EAs. We further predict that this ethnic difference in melatonin production can at least partially explain the ethnic difference in nighttime BP in a bi-ethnic population of young adults.

METHODS

Participants

This study comprised participants from the Georgia Stress and Heart Study, a longitudinal cohort that was established in 1989 to study the development of CV risk factors. The Georgia Stress and Heart Study included 349 AA and 396 EA youth aged 5–16 at the time of recruitment with evaluations conducted every 1–3 years. All participants were recruited from the Southeastern United States and, were apparently healthy, free of any acute or chronic illness, and were not taking any prescription medications based on parental or self-report at the time of testing. Study design, selection criteria, and the criteria to classify participants as AAs or EAs have been described previously.[8,14]

A total of 432 participants (28.4 ± 3.1 years old; 53% AAs and 47% men) took the clinical test of visit 15 between 2008 and 2010. The annualized attrition rate has been <3% per year, which has been primarily due to participants moving out of the region. Data from a total of 150 participants (27.7 ± 3.0 years old; 47% AAs and 54% men), who had both overnight urine samples (n = 170) and validated 24-h ambulatory BP data (n = 253) collected during clinical visit 15, were available for this study. Overnight urine was collected the night before the clinical test and ambulatory BP data were collected the day after the clinical test. Of the 150 participants, 5 were taking antihypertensive medications and 16 were taking oral contraception. The use of medication (either antihypertensive medication or oral contraception) was not associated with nighttime BP or urine melatonin excretion. Furthermore, when participants on medication were excluded from the analyses, the results were virtually unchanged, so results for the entire sample are reported here. The institutional review board at the Medical College of Georgia had given approval for this study. All participants provided written informed consent in accordance with the institutional guidelines.

Anthropometric assessments were obtained during the examination. Height and weight were measured by standard methods using a wall-mounted stadiometer and a digital scale, respectively. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). The participant's smoking status was assessed by the self-reported number of days smoked during the past 30 days, and the number of cigarettes smoked per day. Individuals who smoked at least 5 cigarettes in the past 30 days were considered to be a smoker. Of the 150 participants, 45 were smokers.

BP Measurements

Our procedures for ambulatory BP recordings have previously been described in detail.[8] Briefly, an ambulatory BP monitor was fitted to the nondominant arm (model 90207; SpaceLabs, Redmond, WA). BP measurements were obtained every 20 min during the daytime (0800–2200 h) and every 30 min during the nighttime (12 midnight–0600 h; the narrow fixed time definition of awake–asleep). Transitional periods from 0600 to 0800 h and 2200 to midnight were not included in the analyses. Acceptable readings were defined according to the following criteria: systolic BP (SBP) of at least 70 mm Hg and/or 180 mm Hg or less; diastolic BP (DBP) of at least 40 mm Hg and/or 140 mm Hg or less; pulse pressure of at least 20 mm Hg and/or 140 mm Hg or less; and heart rate of at least 40 beats/min and of 180 beats/min or less. Adequacy of recordings was defined according to the European Society of Hypertension Working Group on Blood Pressure Monitoring[15] as at least 14 readings over the 14 h designated as daytime and at least 6 readings over the 6 h designated as the nighttime.

Urinary melatonin and creatinine measurements

The urine collection protocol involved discarding the last void at bedtime and collecting each subsequent void until the first-morning void. Although considerable variability in melatonin release has been reported, the peak is typically around 3:00. Urine samples were stored at −80 °C until the assay. The participants were also instructed to make a note of the time they went to bed and the period they spent in bed. Urinary aMT6s concentrations were measured using a highly sensitive Enzyme-Linked Immunosorbent Assay Kit (ALPCO, Salem, MA) with a lower aMT6s detection limit of 1.0 ng/ml, an intra-assay coefficient of variation of <9%, and an interassay coefficient of 10%. Urine creatinine was measured by ion-sensitive electrode (NOVA Biomedical), which has an intra-assay coefficient of variation of <3% and an interassay coefficient of 4%. Urine melatonin excretion (UME) was indexed to creatinine excretion, which is calculated as follows: UME = aMT6s concentration (μg/ml)/creatinine concentration (μg/ml).

Statistical analysis

All analyses were performed using STATA software. UME was log transformed due to substantial right skew in the distribution and transformed UME values were used in statistical analysis. Linear regression was used to test whether ethnic differences exist in UME and BP with age, sex, BMI, and smoking as covariates. Linear regression was also used to test the association between UME (as a continuous variable or a categorical tertile scale) and BP with age, sex, ethnicity, BMI, and smoking as covariates. Categorization of UME into tertile groups was performed as a sensitive analysis of the linear relationship between BP and UME in consideration of the skewed distribution of raw UME values. An interaction term between ethnicity and UME was also included in the model to check whether the association between UME and BP was dependent on ethnicity. We further

tested whether the ethnic differences in UME can mediate the ethnic differences in nighttime SBP using the Sobel test.[16] Mediation was considered to present when the ethnic differences in nighttime SBP decreased on addition of UME to the model and the Sobel test gave $P < 0.05$. Covariates in all models included age, sex, BMI, and smoking. Duration in bed did not show a significant association with either UME or SBP, therefore, it was not included as a covariate.

RESULTS

Participant characteristics are presented by ethnicity in Table 1. After adjustment for age, sex, BMI, and smoking, UME differed significantly by ethnicity with AAs having lower UME compared with EAs ($P = 0.002$). AAs had significantly higher nighttime SBP ($P = 0.036$) and DBP than EAs ($P = 0.015$). AAs also had significantly higher daytime DBP than EAs ($P = 0.022$).

There was a significant correlation between UME and nighttime SBP ($r = -0.29$, $P < 0.001$; Figure 1a) as well as daytime SBP ($r = -0.30$, $P < 0.001$; Figure 1b). No significant correlation of UME with either nighttime DBP or daytime DBP was observed (Figure 1c and d). The levels of crude mean nighttime and daytime SBP significantly decreased across UME tertiles (1st tertile: 113.7 ± 8.9 mm Hg; 2nd tertile, 106.3 ± 9.5 mm Hg; 3rd tertile, 105.6 ± 8.4 mm Hg, P value for tertile <0.001; Figure 2a). After including age, sex, ethnicity, BMI, and smoking as covariates into the regression model, the association between UME and nighttime SBP remained significant ($P = 0.026$). No significant interaction between ethnicity and UME on nighttime SBP was identified, indicating the inverse association between UME and nighttime SBP exists in both EAs and AAs. A similar relationship was observed for daytime SBP (1st tertile: 123.9 ± 9.6 mm Hg, 2nd tertile: 118.1 ± 7.9 mm Hg, 3rd tertile: 115.7 ± 9.2 mm Hg, P value for trend <0.001; Figure 2b). However, mean nighttime DBP and daytime DBP were similar across the UME tertiles.

We further tested whether the ethnic differences in UME can explain the ethnic differences in nighttime SBP. As shown in Table 2, the ethnic differences in nighttime SBP decreased on addition of UME to the model (β changes from 3.20 to 2.20 for ethnicity) and the Sobel test was significant ($P = 0.049$), indicating the presence of mediation effects, with UME being able to explain 31.2% of the ethnicity difference in nighttime SBP.

DISCUSSION

To the best of our knowledge, this study is the first to demonstrate the existence of ethnic differences in the endogenous production of melatonin. We observed lower UME levels in AAs compared with EAs. Similar to the previous findings in Caucasians and Asians,[9,10,13,17] this study documents that UME is inversely associated with nighttime SBP in AAs. Importantly, UME was found to be a significant mediator of the ethnic association of nighttime SBP. The present findings support the hypothesis that the ethnic difference in endogenous melatonin production found in this study can, at least in part, explain the established ethnic difference in nighttime BP.

Previous studies have identified ethnic differences in circadian rhythm-related parameters, particularly between AAs and EAs. In fact, differences in the size and the direction of circadian phase shifts have been found between AAs and EAs with an approximate 0.2–0.3 h shorter circadian period in AAs compared with EAs.[18,19] AAs are more likely to report short sleep duration and poorer objective and subjective sleep quality after adjustment for several sociodemographic and health characteristics.[20,21] The presence of abnormal diurnal BP variation such as a lack of nocturnal fall in BP is more frequent in AAs compared with EAs.[6,22] Despite these collective evidence of ethnic disparities in circadian rhythmicity, we are unaware of any studies to date that evaluated the ethnic difference in the endogenous production of melatonin, a primary key hormone responsible for synchronizing the circadian

Table 1. Demographic and blood pressure characteristics of participants

	European Americans	African Americans	*P*
N	79	71	
Females (%)	43.0	49.3	NS
Age (yr)	27.6 ± 3.2	27.9 ± 2.8	NS
BMI* (kg/m^2)	27.2 ± 6.8	27.4 ± 6.9	NS
Duration in bed (h)	7.7 ± 1.7	7.6 ± 1.8	NS
UME+	0.34 ± 0.33	0.26 ± 0.20	0.002
Nighttime SBP+ (mm Hg)	107.2 ± 9.0	110.0 ± 10.2	0.036
Nighttime DBP+ (mm Hg)	61.0 ± 6.5	64.1 ± 8.4	0.015
Daytime SBP+ (mm Hg)	118.7 ± 9.1	119.8 ± 10.0	NS
Daytime DBP+ (mm Hg)	72.3 ± 7.7	75.2 ± 7.8	0.022

Values are mean ± standard deviation. Abbreviations: BMI, body mass index; DBP: brachial diastolic blood pressure; SBP, brachial systolic blood pressure; UME, urinary 6-sulfatoxymelatonin excretion.

*For the test of race difference, age and gender were included in the model as covariates.

+For the test of race difference, age, gender, BMI, and smoking were included in the model as covariates.

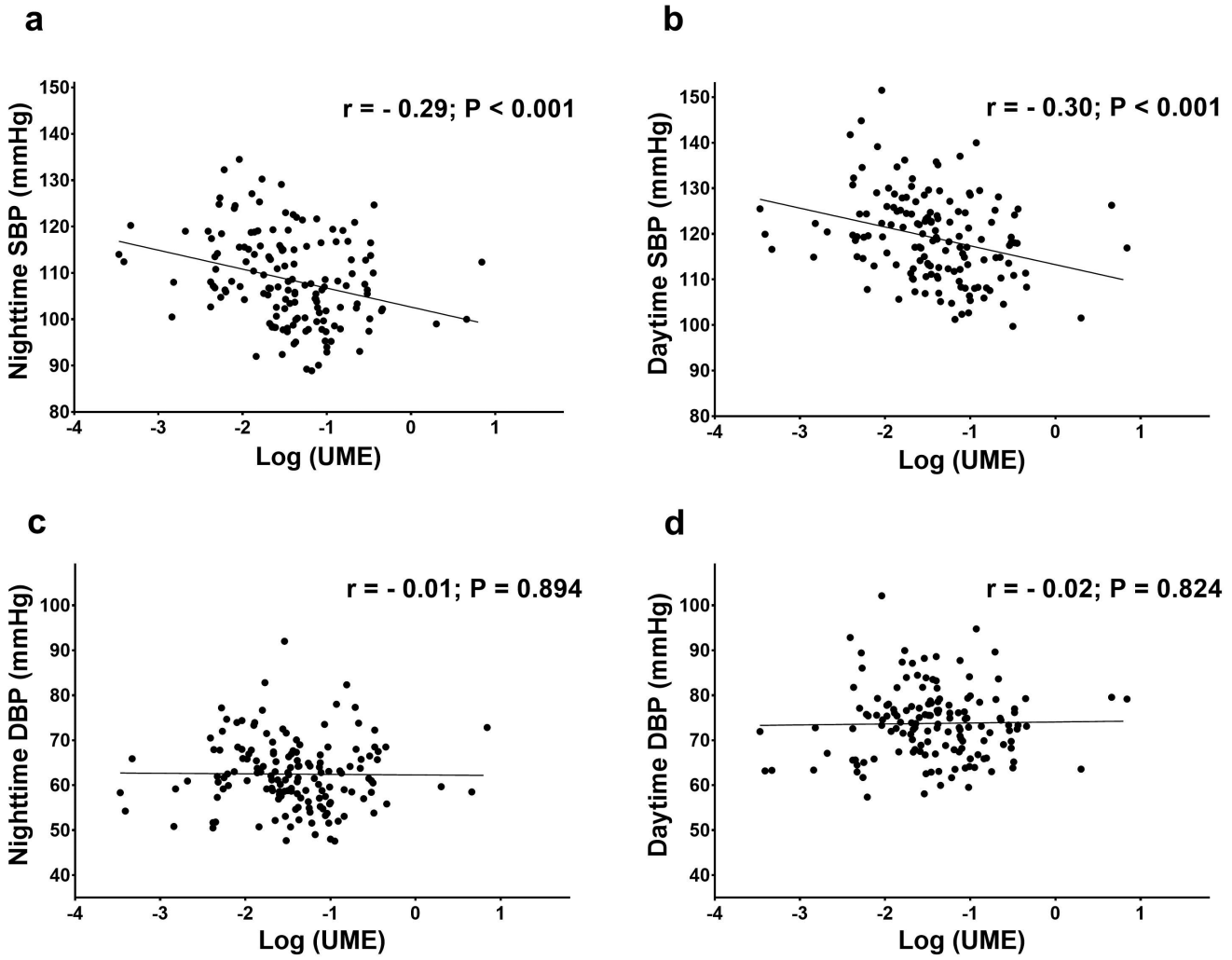

Figure 1. Correlation between log-transformed urinary 6-sulfatoxymelatonin excretion (UME) and nighttime systolic blood pressure (SBP) (**a**), daytime SBP (**b**), nighttime diastolic blood pressure (DBP) (**c**) and daytime DBP (**d**).

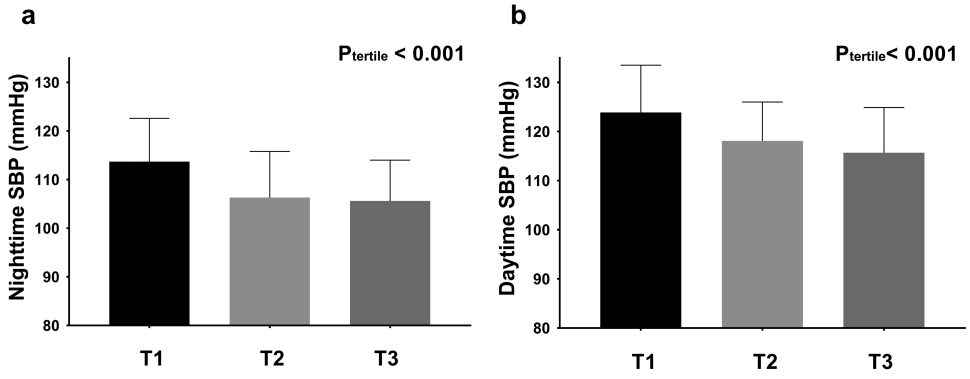

Figure 2. Associations of tertiles of urinary 6-sulfatoxymelatonin excretion (UME) with nighttime (**a**) and daytime (**b**) systolic blood pressure (SBP); tertile 1 (**T1**): UME < 0.188, *n* = 50; tertile 2 (**T2**): 0.188 ≤ UME < 0.323, *n* = 50; tertile 3 (**T3**): UME ≥ 0.323, *n* = 50. Error bars indicate standard deviations. The represented values are crude mean values.

rhythm. Importantly, we observed AAs exhibit significantly lower excretion of melatonin compared to EAs regardless of age and sex. It is unknown whether this decreased melatonin secretion in AAs is a result of environmental factors or is of genetic origin. Additional studies are needed to clarify the mechanisms of decreased melatonin secretion in AAs.

Table 2. Mediation analysis of UME for the ethnicity difference in nighttime SBP

Without mediator (UME)*					
Dependent variables	**Independent variables**	**Beta (95% CI)**	***P***		
Nighttime SBP (mm Hg)	Ethnicity (AA vs. EA)	3.20 (0.27, 6.13)	0.036		
With mediator (UME)*					
Dependent variables	**Independent variables**	**Beta**	***P***	**Mediation effect**	
				% Difference explained	***P***
Nighttime SBP (mm Hg)	Ethnicity (AA vs. EA)	2.20 (–0.82, 5.22)	0.163	31.2	0.049
	UME (tertiles)	–2.33 (–4.35, –0.30)	0.026		

Abbreviations: AA, African American; EA, European American; SBP: brachial systolic blood pressure; UME, urinary 6-sulfatoxymelatonin excretion.

*Age, gender, BMI, and smoking were included in the model as covariates.

In addition to its role of regulating circadian rhythms, melatonin appears to be involved in BP regulation.[23] Impaired melatonin secretion has not only been identified in patients with hypertension who exhibit a nocturnal non-dipping pattern and it has also been linked to a reduced magnitude of nocturnal fall in SBP in the general population.[9,10,13,17] This study confirms these previous findings in Caucasians and Asians as well as extending the link of melatonin with SBP into AAs. This inverse relationship between nighttime SBP and UME is also supported by marked and consistent differences in SBP across UME tertiles; nighttime SBP was higher in the lowest UME group and lowest in the highest UME group with the mean group difference of 8.1 mm Hg in nighttime SBP (Figure 2a).

Although the mechanisms are not clear, the influence of melatonin on circadian BP profiles may result from its modulating role of autonomic nervous activity with sympathetic inhibition and parasympathetic activation.[24,25] Melatonin has direct effects on peripheral arteries that may also be a contributor to favorable nocturnal BP patterns through its antioxidative properties and its interaction with vasodilatory and vasoconstrictive pathways such as nitric oxide and cytosolic Ca^{2+} in endothelial and smooth muscle cells.[23] Interestingly, UME also shows a significant relationship with daytime SBP (Figure 1b). No causal relationship can be extrapolated from our results regarding whether decreased melatonin secretion overnight may have affected daytime BP levels, or increased CV load from increased BP levels during the day have affected the nighttime melatonin secretion. Nonetheless, our findings may suggest that daytime SBP, a conventional way of monitoring BP, can be an indicator of decreased melatonin secretion in young adults.

Another finding that should be noted in this study is that nocturnal melatonin excretion was not associated with either daytime or nighttime DBP (Figure 1c and d). This is consistent with a recent study in older individuals.[17] In contrast, previous clinical trials using oral melatonin have observed the potential BP-lowering effects of melatonin on both nighttime SBP and DBP.[26,27] The main determinant of isolated hypertension, elevated SBP without a concomitant increase in DBP, is thought to be hyperkinetic circulation as a result of increased sympathetic activity in young individuals[28] whereas atherosclerotic changes such as stiff arteries are mainly responsible for isolated hypertension in older adults.[29] Thus, we hypothesize that the effect of endogenous melatonin on BP regulation in young adults is primarily through its modulation on autonomic activity. The lack of association between melatonin and DBP we observed may be due to the lack of relevance of DBP with the autonomic nervous system. This hypothesis, however, will require further investigation.

Ethnic differences in diurnal BP patterns have been well documented. In general, AAs having a higher nighttime BP and a blunted nocturnal decline in comparison with EAs.[6,7] The ethnic differences in nocturnal BP patterns shown in this study are directly in line with these previous observations.[6,7] Several factors have been hypothesized to account for the observed ethnic differences including genetic factors, obesity, social economic status, psychosocial stress, and sodium intake.[30] In this study, we demonstrated that the difference in endogenous melatonin excretion between AAs and EAs could be another contributor to the ethnic differences in nighttime SBP. Specifically, our mediation analysis indicates that 31.2% of the ethnicity difference in nighttime SBP could be explained by UME (Table 2). Understanding the environmental and pathogenetic factors contributing to the decreased melatonin excretion in AAs will provide new therapeutic targets for prevention of hypertension in this high-risk population. Studies investigating the effects of modifying melatonin levels on nighttime SBP in AAs, using strategies such as administration of exogenous melatonin or changing environmental factors are also warranted. It is important to note that when UME was added to the model, race was not significantly associated with nighttime SBP anymore. This may be attributed to the relatively small sample size of our current study. Furthermore, although we observed that endogenous melatonin excretion as a significant contribution to the ethnic difference in nighttime SBP, these results do not confirm biological mediation and should be validated by prospective interventional studies.

Clinical significance

The diurnal pattern of BP is an important factor when determining CV disease risk.[1] Elevated nighttime BP predicts target organ damage and is an independent risk factor of heart disease.[31–33] There is ample evidence for substantial health disparities between AAs and EAs in CV disease and CV-associated risk factors. The identification of specific factors that contribute to hypertension is critical to reduce CV-related morbidities, especially in populations at increased risk of CV disease, such as AAs. Our findings provide important evidence for possible involvement of decreased endogenous melatonin secretion in explaining the higher nighttime SBP observed in AAs. This information provides an important piece of evidence that melatonin, a hormone responsible for circadian rhythm, plays a role in ethnic differences in circadian BP regulation. Thus, melatonin may represent a novel therapeutic target for preventing the onset and development of hypertension in AAs that are particularly prone to nocturnal hypertension.

Conclusion

This study has identified that AAs exhibit significantly lower urinary melatonin secretion compared with EAs. The urinary melatonin secretion was inversely associated with nighttime and daytime BP in AAs with adjustment of age, sex, and BMI. Importantly, the ethnic difference in melatonin excretion was found to partly explain the established ethnic difference in nighttime SBP, suggesting a clinical value of melatonin in the management of hypertension in AAs.

ACKNOWLEDGMENT

Supported in part by National Heart, Lung, and Blood Institute Grant (P01 HL069999 to G.A.H., D.M.P., J.S.P.).

DISCLOSURE

None to declare.

REFERENCES

1. Pickering TG, James GD. Determinants and consequences of the diurnal rhythm of blood pressure. *Am J Hypertens* 1993; 6:166S–169S.
2. Smolensky MH, Hermida RC, Portaluppi F. Circadian mechanisms of 24-hour blood pressure regulation and patterning. *Sleep Med Rev* 2017; 33:4–16.
3. Salles GF, Reboldi G, Fagard RH, Cardoso CR, Pierdomenico SD, Verdecchia P, Eguchi K, Kario K, Hoshide S, Polonia J, de la Sierra A, Hermida RC, Dolan E, O'Brien E, Roush GC; ABC-H Investigators. Prognostic effect of the nocturnal blood pressure fall in hypertensive patients: the ambulatory blood pressure collaboration in patients with hypertension (ABC-H) meta-analysis. *Hypertension* 2016; 67:693–700.
4. Shen J, Li ZM, He LZ, Deng RS, Liu JG, Shen YS. Comparison of ambulatory blood pressure and clinic blood pressure in relation to cardiovascular diseases in diabetic patients. *Medicine (Baltimore)* 2017; 96:e7807.
5. Turner JR, Viera AJ, Shimbo D. Ambulatory blood pressure monitoring in clinical practice: a review. *Am J Med* 2015; 128:14–20.
6. Muntner P, Lewis CE, Diaz KM, Carson AP, Kim Y, Calhoun D, Yano Y, Viera AJ, Shimbo D. Racial differences in abnormal ambulatory blood pressure monitoring measures: results from the coronary artery risk development in young adults (CARDIA) study. *Am J Hypertens* 2015; 28:640–648.
7. Profant J, Dimsdale JE. Race and diurnal blood pressure patterns. A review and meta-analysis. *Hypertension* 1999; 33:1099–1104.
8. Wang X, Poole JC, Treiber FA, Harshfield GA, Hanevold CD, Snieder H. Ethnic and gender differences in ambulatory blood pressure trajectories: results from a 15-year longitudinal study in youth and young adults. *Circulation* 2006; 114:2780–2787.
9. Zeman M, Dulková K, Bada V, Herichová I. Plasma melatonin concentrations in hypertensive patients with the dipping and non-dipping blood pressure profile. *Life Sci* 2005; 76:1795–1803.
10. Jonas M, Garfinkel D, Zisapel N, Laudon M, Grossman E. Impaired nocturnal melatonin secretion in non-dipper hypertensive patients. *Blood Press* 2003; 12:19–24.
11. Arendt J, Bojkowski C, Franey C, Wright J, Marks V. Immunoassay of 6-hydroxymelatonin sulfate in human plasma and urine: abolition of the urinary 24-hour rhythm with atenolol. *J Clin Endocrinol Metab* 1985; 60:1166–1173.
12. Kovács J, Brodner W, Kirchlechner V, Arif T, Waldhauser F. Measurement of urinary melatonin: a useful tool for monitoring serum melatonin after its oral administration. *J Clin Endocrinol Metab* 2000; 85:666–670.
13. Obayashi K, Saeki K, Iwamoto J, Okamoto N, Tomioka K, Nezu S, Ikada Y, Kurumatani N. Nocturnal urinary melatonin excretion is associated with non-dipper pattern in elderly hypertensives. *Hypertens Res* 2013; 36:736–740.
14. Su S, Wang X, Pollock JS, Treiber FA, Xu X, Snieder H, McCall WV, Stefanek M, Harshfield GA. Adverse childhood experiences and blood pressure trajectories from childhood to young adulthood: the Georgia stress and Heart study. *Circulation* 2015; 131:1674–1681.
15. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P; European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003; 21:821–848.
16. Sobel ME. Asymptotic confidence intervals for indirect effects in structural equation models. In: *Leinhardt SSociological Methodology*. Washington, DC: American Sociological Association; 1982.
17. Obayashi K, Saeki K, Tone N, Kurumatani N. Relationship between melatonin secretion and nighttime blood pressure in elderly individuals with and without antihypertensive treatment: a cross-sectional study of the HEIJO-KYO cohort. *Hypertens Res* 2014; 37:908–913.
18. Eastman CI, Suh C, Tomaka VA, Crowley SJ. Circadian rhythm phase shifts and endogenous free-running circadian period differ between African-Americans and European-Americans. *Sci Rep* 2015; 5:8381.
19. Czeisler CA, Duffy JF, Shanahan TL, Brown EN, Mitchell JF, Rimmer DW, Ronda JM, Silva EJ, Allan JS, Emens JS, Dijk DJ, Kronauer RE. Stability, precision, and near-24-hour period of the human circadian pacemaker. *Science* 1999; 284:2177–2181.
20. Jean-Louis G, Grandner MA, Youngstedt SD, Williams NJ, Zizi F, Sarpong DF, Ogedegbe GG. Differential increase in prevalence estimates of inadequate sleep among black and white Americans. *BMC Public Health* 2015; 15:1185.
21. Tomfohr L, Pung MA, Edwards KM, Dimsdale JE. Racial differences in sleep architecture: the role of ethnic discrimination. *Biol Psychol* 2012; 89:34–38.
22. Yamasaki F, Schwartz JE, Gerber LM, Warren K, Pickering TG. Impact of shift work and race/ethnicity on the diurnal rhythm of blood pressure and catecholamines. *Hypertension* 1998; 32:417–423.
23. Pechanova O, Paulis L, Simko F. Peripheral and central effects of melatonin on blood pressure regulation. *Int J Mol Sci* 2014; 15:17920–17937.
24. K-Laflamme A, Wu L, Foucart S, de Champlain J. Impaired basal sympathetic tone and alpha1-adrenergic responsiveness in association with the hypotensive effect of melatonin in spontaneously hypertensive rats. *Am J Hypertens* 1998; 11:219–229.
25. Paulis L, Simko F. Blood pressure modulation and cardiovascular protection by melatonin: potential mechanisms behind. *Physiol Res* 2007; 56:671–684.

26. Grossman E, Laudon M, Yalcin R, Zengil H, Peleg E, Sharabi Y, Kamari Y, Shen-Orr Z, Zisapel N. Melatonin reduces night blood pressure in patients with nocturnal hypertension. *Am J Med* 2006; 119:898–902.
27. Scheer FA, Van Montfrans GA, van Someren EJ, Mairuhu G, Buijs RM. Daily nighttime melatonin reduces blood pressure in male patients with essential hypertension. *Hypertension* 2004; 43:192–197.
28. Saladini F, Palatini P. Isolated systolic hypertension in young individuals: pathophysiological mechanisms, prognostic significance, and clinical implications. *High Blood Press Cardiovasc Prev* 2017; 24:133–139.
29. Franklin SS, Gustin W IV, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation* 1997; 96:308–315.
30. Harshfield G. Ethnic differences in childhood blood pressure. In: Flynn J, Ingelfinger JR, Portman RJ (ed), *Pediatric Hypertension*. Springer: New York Dordrecht Heidelberg London, 2011.
31. Cuspidi C, Meani S, Salerno M, Valerio C, Fusi V, Severgnini B, Lonati L, Magrini F, Zanchetti A. Cardiovascular target organ damage in essential hypertensives with or without reproducible nocturnal fall in blood pressure. *J Hypertens* 2004; 22:273–280.
32. Bianchi S, Bigazzi R, Baldari G, Sgherri G, Campese VM. Diurnal variations of blood pressure and microalbuminuria in essential hypertension. *Am J Hypertens* 1994; 7:23–29.
33. Draman MS, Dolan E, van der Poel L, Tun TK, McDermott JH, Sreenan S, O'Brien E. The importance of night-time systolic blood pressure in diabetic patients: Dublin Outcome Study. *J Hypertens* 2015; 33:1373–1377.