Age-Related Changes of Circadian Rhythms and Sleep-Wake Cycles

In-Young Yoon, MD, PhD, Daniel F. Kripke, MD,* Jeffrey A. Elliott, PhD,* Shawn D. Youngstedt, PhD,* Katharine M. Rex, BA,* and Richard L. Hauger, MD†*

OBJECTIVES: To compare relationships between the sleep-wake cycle and endogenous circadian rhythms in young and older adults and to examine correlates between evening naps and circadian rhythms in older adults.

DESIGN: For 1 week of home recording, subjects wore wrist-activity monitors and kept daily sleep logs. After the home monitoring, subjects entered the laboratory on a 90-minute sleep-wake schedule and were monitored on this schedule for at least 30 hours.

SETTING: Community living and laboratory.

PARTICIPANTS: Sixty-seven young adults, aged 18 to 32, and 56 older adults, aged 60 to 75, who were healthy and had few sleep complaints.

MEASUREMENTS: Times of nocturnal sleep, out-of-bed napping, and illumination were obtained at home. Sleep propensity and oral body temperature (OBT) were measured in the laboratory, along with circadian rhythms of cortisol and 6-sulfatoxymelatonin (aMT6s, assayed from urine samples collected every 90 minutes).

RESULTS: Home sleep times and illumination acrophases (fitted peak times) were advanced in older adults. The phase angles (time intervals) between onset of aMT6s and sleep onset were not changed in older adults, but sleep offset was more advanced than acrophase and offset of aMT6s with aging. Acrophases of cortisol and sleep propensity were advanced in older adults to the same extent as sleep times, but OBT was less advanced than sleep times. Older adults who took evening naps showed more advanced sleep offset and circadian rhythms of aMT6s, but there were no differences in the phase angles of sleep onset and circadian rhythms of aMT6s and cortisol compared with older adults who did not take evening naps.

CONCLUSION: Measuring different circadian markers suggested different phase relationships between the sleep-wake cycle and endogenous circadian rhythms in aging. Early awakening in older adults cannot be explained simply by a relative phase advance of the circadian system. Evening naps and advanced illumination may play a role in the advance of the circadian system in aging. **J Am Geriatr Soc 51:1085–1091, 2003.**

Key words: sleep-wake; circadian; aging; melatonin; naps

Older people often go to bed early at night and wake up early in the morning.[1,2] The advance of sleep time in older people has been explored in reference to endogenous circadian rhythms. Although it is generally accepted that older people show a phase advance of circadian rhythms compared with young people,[3,4] some studies have reported no phase advance of core body temperature (CBT)[5] or melatonin acrophase[6] in older people. There has also been some controversy about changes of phase relationships between sleep time and circadian rhythms in older people. In one study,[7] the interval between the CBT fitted minimum and awakening time was not different between young and older subjects. The interval was 85 minutes for the young group and 95 minutes for the older group. A similar result was replicated in another study, with the awakening time being an average of 3 hours after the CBT minimum in both young and older adults.[8] However, changes of the phase relationship were reported in a study with larger aging samples[4] and in a study using plasma melatonin as a circadian marker.[9] In both those studies, the intervals between the circadian markers and the awakening time were shorter in older adults than in young adults. Thus, older adults were waking up at earlier circadian phases. However, sex differences between the samples might have partly confounded the latter studies,[4,9] in that the young samples consisted only of men, whereas the older samples had equivalent numbers of men and women. Thus, there has been

From the *Department of Psychiatry and Sam and Rose Stein Institute for Research on Aging, and †VA Healthcare System and Department of Psychiatry, University of California at San Diego, La Jolla, California.

This study was supported by National Institutes of Health Grant NHLBI HL 61280 and the Yong-In Mental Hospital, Yong-In, Korea. R. Hauger is supported by a Veterans Affairs (VA) Merit Review grant and the VA Mental Illness Research, Education and Clinical Center of VISN22. Presented at the Associated Professional Sleep Societies 16th Annual Meeting, Seattle, Washington, June 2002, and the Society for Light Treatment and Biological Rhythms 14th Annual Meeting, San Diego, California, June 2002.

Address correspondence to Daniel F. Kripke, MD, Department of Psychiatry, 0667, University of California at San Diego, 9500 Gilman Drive, La Jolla, CA 92093. E-mail: dkripke@ucsd.edu

0002-8614/03/$15.00

some doubt about whether the relationship between sleep and the circadian system changes with aging.

Napping in the evening is a common behavior in older adults.[10,11] We found that evening napping in older adults was related to early morning awakening,[12] but it was unclear whether evening napping might be a cause or an effect of circadian system phase advance.

An ultra-short sleep-wake cycle is one of the methods that differentiate circadian rhythms from sleep and posture effects in evaluating hormone secretion and body temperature.[13] With an ultra-short sleep-wake cycle, waking and sleep-recumbent intervals become evenly distributed such that masking effects of sleep and recumbency tend to be equalized around the clock.[14,15]

To elucidate the relationship between the sleep-wake cycle and endogenous circadian rhythms in aging, we measured 6-sulfatoxymelatonin (aMT6s) and cortisol in large samples using an ultra-short sleep-wake cycle. In addition, oral body temperature and sleep propensity were evaluated. The correlates between evening naps and unmasked circadian rhythms in the older adults were also investigated.

METHODS

Subjects

Sixty-nine young adults, 44 women and 25 men aged 18 to 32 (mean ± standard deviation (SD) = 23.7 ± 3.8) and 59 older adults, 37 women and 22 men aged 60 to 75 (66.2 ± 4.9) participated in this study. Most of these subjects had been included in a previous report.[12] Because these observations were part of a study of exercise effects on circadian phase, subjects were selected for good general health and for regular exercise. Subjects were in the top 5th percentile of aerobic fitness for their respective ages as measured using maximal oxygen uptake (VO_{2peak}) testing. They had no acute mental or physical problems. No severe sleep complaints were observed using the Pittsburgh Sleep Quality Inventory (mean = 3.8 ± 2.8), but about one-fourth of all subjects met a threshold criterion of 5 for poor sleep.[16] Depression was assessed using the Center for Epidemiologic Studies—Depression (CES-D) scale,[17] and seven of the young subjects scored 16 or more, which is considered to be suggestive of major depression. None of the older subjects scored 16 or more on CES-D. The institutional review board of the University of California at San Diego approved this study. Each subject gave written informed consent.

Procedures

Home Monitoring

For 1 week of home recording, subjects were asked to maintain stable sleep-wake schedules. They wore the Actillume wrist-activity monitor (AMI, Ardsley, NY) and kept daily sleep logs during this period. We obtained six or seven 24-hour data records of wrist-activity and illumination data from 84% of the subjects (107/128), 5 days of data from 17 subjects, 4 days of data from three subjects, and 3 days of data from one subject.

Laboratory Recording

Ultra-short sleep-wake cycle. After 1 week of home monitoring, subjects entered the laboratory at 9:30 a.m. They started a 90-minute sleep-wake schedule, which consisted of 30 minutes of sleep, followed by a 60-minute awake period (90-minute day). They remained on this schedule for at least 30 hours baseline before undergoing randomized exercise or bright light (to determine the phase response curves). This report concerns only the data obtained during a 24-hour baseline period. During each 30-minute sleep interval, subjects lay down in a dark (<0.1 lux) bedroom and were asked to sleep. During the 60-minute wake intervals, the subject rooms were maintained at 30 to 50 lux average eye-level illumination, and subjects got out of bed and were asked to remain awake. To monitor sleep-wake cycles and to evaluate the circadian modulation of sleep during the 90-minute day, subjects wore an Actillume wrist-activity monitor. At the beginning of each 60-minute wake interval, oral body temperature (OBT) was measured with a high-resolution electronic oral thermometer. Urine samples were also collected every 90 minutes during the wake periods.

Hormone assay Each urine sample was measured for volume, and aliquots (2 mL) were frozen for assay. Urinary aMT6s, the major metabolite of melatonin, and free cortisol were assayed from each urine sample. Urinary aMT6s was assayed with Bühlmann enzyme immunosorbent assay kits (ALPCO, Ltd, Windham, NH). At a sample dilution of 1:200, the analytic sensitivity of this assay is less than 0.35 ng/mL, and intra- and interassay coefficients of variation are 3.3% and 6.7%, respectively. Urinary free cortisol was measured using a double antibody cortisol radioimmunoassay (Diagnostic System Laboratories, Webster, TX) with a sensitivity of 0.3 g/dL and intra- and interassay coefficients of variation of 8.4% and 9.1%, respectively.

Data Analysis

Sleep-wake cycle and illumination at home: circadian rhythms in the laboratory. Automatic home-sleep scoring was done using Action3 software using validated algorithms.[18] The authors edited this automatic sleep scoring with the assistance of 24-hour sleep logs and illumination data. In evaluating the sleep-wake cycle at home, the in-bed sleep-onset time, sleep-offset time, total sleep time (TST), wake time after sleep onset (WASO), and timing of out-of-bed naps were estimated from the edited sleep scoring. Twenty-four-hour cosine fits were applied to the $\log_{10}$[lux] home illumination data. The minimum illumination was set to $\log_{10}$[lux] = 0, because biological effects of less than 1 lux were considered negligible.[19] Automatic scoring of the sleep-wake state in the laboratory was done using the same algorithms used in the home-sleep scoring. During each 30-minute sleep interval at the laboratory, TST was calculated. Sleep propensity was defined as the TST during each 30-minute sleep interval. Twenty-four-hour cosine fits were also applied to laboratory aMT6s, cortisol, OBT, and TST values for all 30-minute lights-out intervals. These data were analyzed from 3:00 p.m. (4.5 hours after the 90-minute day started) to 3:00 p.m. of the next day. Acrophases, amplitudes, and mesors (24-hour-cosine mean) were computed from the 24-hour-cosine fits. The times of aMT6s onset and offset were defined as the times of upward and downward crossing, respectively, of the mesors of aMT6s cosine fits. Log-transformed values of the amplitudes and mesors of aMT6s were used because of their

skewed interindividual variations. Phase dispersion was computed from the acrophases of aMT6s and cortisol in both age groups and was defined as the absolute difference in hours (advance or delay) between each individual's acrophase and the median acrophase for each age group.[6]

Phase relationships. To explore phase relationships between the sleep-wake cycle at home and circadian rhythms of aMT6s and cortisol in the laboratory, phase angles were estimated. The phase angles of the onset, acrophase, and offset of aMT6s rhythm to sleep onset and sleep offset were calculated. The phase angles of the acrophase of cortisol rhythm to sleep onset and sleep offset were also calculated. The phase angles between sleep times and the sleep propensity acrophase were calculated similarly.

Statistical analysis. We used SPSS 9.0 for Windows for statistical analyses (SPSS Inc., Chicago, IL). Cosine estimates accounting for less than 50% of the variance (goodness of fit) were excluded from further analyses. The Kolmogorov-Smirnov test was used to confirm normality. The parameters for evaluating the sleep-wake cycle, circadian rhythms, and phase angles were compared between young and older adults using two-tailed *t* tests. A similar comparison was repeated between older adults with and without evening naps. Pearson correlation coefficients were calculated to determine the relationships between the sleep-wake cycle and circadian rhythms of aMT6s and cortisol, with the Spearman used for highly skewed data. The significance criterion was defined at $P < .05$ for two-tailed tests.

RESULTS

Sleep-Wake Cycle at Home and Circadian Rhythms of aMT6s and Cortisol in the Laboratory

All the subjects showed cosine goodness of fit of more than 50% in aMT6s rhythms, but five subjects (two young and three older) showed goodness of fit of less than 50% in cortisol rhythms. These five subjects were excluded from further analysis. Thus, the circadian rhythms of aMT6s and cortisol were analyzed in 67 young adults and 56 older adults. The mean goodness of fit of aMT6s and cortisol were 85.0 ± 7.7% and 75.0 ± 9.5%, respectively. A comparison of nocturnal sleep and circadian rhythms between young and older adults is displayed in Table 1. Sleep-onset and sleep-offset times were earlier in the older group, and TST was decreased and WASO increased in the older group (all $P < .001$). The onset times and acrophases of aMT6s excretion were advanced in older adults ($P = .002$ and $P = .004$, respectively), but there was no difference in the offset times of aMT6s ($P = .245$). The durations of aMT6s excretion were increased in older adults ($P = .015$). The acrophases of cortisol excretion were advanced in older adults ($P < .001$). The amplitudes of melatonin and cortisol excretion were decreased in older adults ($P < .001$ and $P = .041$, respectively). The mesor of aMT6s excretion was decreased in older adults ($P < .001$), but the mesor of cortisol excretion was not changed in older adults ($P = .409$). The amplitudes and mesor of aMT6s were highly correlated in both age groups (young, $r = 0.981$, $P < .001$; older, $r = 0.986$, $P < .001$). There was no difference in phase dispersion between young and older adults in aMT6s or cortisol. There was no sex difference in acrophase, amplitude, or mesor of aMT6s and cortisol excretion in young or older adults, although acrophases of aMT6s and cortisol tended to be a little more advanced in young and older women than in young and older men. Seven young adults with CES-D scores of 16 or more showed no difference in the onset, acrophase, and offset of aMT6s or acrophase of cortisol compared with the other 60 young adults.

Circadian Rhythms of Illumination at Home, and Sleep Propensity and Oral Body Temperature (OBT) in the Laboratory

Table 2 shows circadian parameters of illumination, sleep propensity, and OBT. Like the cosinor analyses of aMT6s

Table 1. Parameters of Nocturnal Sleep at Home and Circadian Rhythms of 6-Sulphatoxymelatonin (aMT6s) and Cortisol in the Laboratory of Young and Older Adults

Parameter	Young (n = 67)	Older (n = 56)	*P*-value
	Mean ± Standard Deviation		
Sleep onset time	00:23 ± 1:12	22:51 ± 1:19	<.001
Sleep offset time	08:11 ± 1:22	06:32 ± 1:06	<.001
Total sleep time, minutes	421.7 ± 48.3	367.1 ± 51.6	<.001
Wake time after sleep onset, minutes	45.08 ± 20.29	94.67 ± 54.43	<.001
aMT6s onset	23:10 ± 1:41	22:01 ± 2:14	.002
aMT6s acrophase	03:39 ± 1:30	03:02 ± 1:40	.004
aMT6s offset	8:29 ± 2:04	8:04 ± 1:45	.245
aMT6s duration, hours	9.32 ± 1.47	10.05 ± 1.84	.015
Log_{10} aMT6s amplitude, ng/h	2.91 ± 0.33	2.53 ± 0.37	<.001
Log_{10} aMT6s mesor, ng/h	2.79 ± 0.34	2.43 ± 0.36	<.001
Phase dispersion of aMT6s	1.25 ± 0.84	1.30 ± 1.09	.736
Cortisol acrophase	09:58 ± 1:46	08:28 ± 1:24	<.001
Cortisol amplitude, μg/h	4.06 ± 2.29	3.23 ± 2.11	.041
Cortisol mesor, μg/h	3.89 ± 1.82	3.60 ± 2.09	.409
Phase dispersion of cortisol	1.41 ± 1.07	1.11 ± 0.89	.098

Table 2. Circadian Rhythms of Illumination, Sleep Propensity, and Oral Body Temperature

Parameter	Young	Older	*P*-value
	Mean ± Standard Deviation		
Illumination	n = 64	n = 56	
Acrophase	14:09 ± 0:53	13:22 ± 0:48	<.001
Amplitude, log_{10}lux	1.20 ± 0.22	1.21 ± 0.26	.694
Mesor, log_{10}lux	1.11 ± 0.23	1.13 ± 0.21	.570
Sleep propensity	n = 42	n = 27	
Acrophase	6:35 ± 2:11	5:10 ± 1:49	.007
Amplitude, minutes	3.96 ± 1.87	5.64 ± 2.21	.001
Mesor, minutes	22.46 ± 2.60	17.31 ± 3.17	<.001
Oral body temperature	n = 53	n = 51	
Acrophase	15:49 ± 2:13	15:27 ± 2:06	.378
Amplitude	0.28 ± 0.12	0.29 ± 0.12	.818
Mesor	36.38 ± 0.24	36.24 ± 0.23	.002

Note: Subjects with goodness of fit of greater than 50% were included.

and cortisol, subjects with goodness of fit of less than 50% were excluded. The acrophases of illumination were advanced by 47 minutes in older adults (n = 56) compared with those of young adults (n = 64) ($P < .001$). The acrophases of sleep propensity were also advanced by 85 minutes in older 27 adults ($P = .007$) compared with those of 42 young and 27 older subjects. The acrophases of OBT were advanced by 22 minutes in older adults, but there was no statistical difference between young and older groups (53 young and 51 older subjects). Results were similar including those acrophases with poor goodness of fit.

Phase Angles

The phase angles between the sleep times and circadian rhythms of aMT6s, cortisol, and sleep propensity are shown in Table 3. There was no significant difference in the phase angle of aMT6s onset to sleep onset in young and older subjects. The phase angle of sleep onset to aMT6s acrophase was larger, and the phase angle of aMT6s acrophase to sleep-offset time was smaller in older subjects than in young subjects. The phase angle of sleep offset to aMT6s offset was increased in older adults. Phase angles between sleep times and cortisol acrophase did not differ in older and young subjects. The phase angle between aMT6s and cortisol acrophases was decreased in older subjects. There was no difference between young and older subjects in the phase angles between home sleep times and laboratory sleep propensity acrophases.

Older Adults Who Did and Did Not Take Evening Naps

Evening naps were defined as out-of-bed sleep occurring from 2 hours to just before bedtime. Of 56 older subjects, 29 showed at least one evening nap in the 1-week home recording. The older subjects who took evening naps showed earlier sleep-offset times and a more-advanced acrophase of the aMT6s rhythm than older subjects who did not take evening naps (Table 4). The onset and offset times of aMT6s were likewise marginally more advanced in the older subjects who took evening naps ($P = .093$, $P = .083$, two-tailed, respectively). There was no significant difference in the acrophase of the cortisol rhythm between the older adults who did and did not take evening naps, and no difference was observed in any of the phase angles between these two groups (Table 4). There was no correlation between minutes of evening napping and the phase angle of aMT6s onset to sleep onset ($r = 0.23$, $P = .226$). Subjects who did and did not take evening naps also showed no difference in the acrophases of illumination, OBT, and sleep propensity.

Correlations Between the Sleep-Wake Cycle and Circadian Rhythms of aMT6s and Cortisol

Table 5 displays correlations between the sleep-wake cycle and circadian rhythms. In both age groups, there were modest correlations between sleep-onset or -offset times measured at home and acrophases of aMT6s or cortisol excretion measured in the laboratory. Modest correlations were observed between sleep-onset times and aMT6s onset, and sleep-offset times and aMT6s offset. Higher correlations were observed between sleep-offset time and aMT6s

Table 3. Phase Angles between Sleep Times and Circadian Rhythms of 6-Sulphatoxymelatonin (aMT6s), Cortisol, and Sleep Propensity (SP) of Young and Older Adults

Phase Angles (hrs)	Young (n = 67)	Older (n = 56)	*P*-value
	Mean ± Standard Deviation		
aMT6s onset to sleep onset	1.22 ± 1.65	0.81 ± 2.15	.243
Sleep onset to aMT6s acrophase	3.25 ± 1.48	4.19 ± 1.67	.001
aMT6s acrophase to sleep offset	4.54 ± 1.28	3.51 ± 1.35	<.001
Sleep offset to aMT6s offset	0.30 ± 1.78	1.54 ± 1.41	<.001
Sleep onset to cortisol acrophase	9.58 ± 1.52	9.63 ± 1.47	.847
Sleep offset to cortisol acrophase	1.78 ± 1.48	1.93 ± 1.25	.539
aMT6s acrophase to cortisol acrophase	6.32 ± 1.42	5.44 ± 1.37	<.001
Sleep onset to SP acrophase*	6.21 ± 2.35	6.27 ± 2.27	.918
SP acrophase to sleep offset*	1.61 ± 2.15	1.39 ± 1.67	.645

*Subjects with goodness of fit of greater than 50% were included (young, n = 42; older, n = 27).

Table 4. Sleep Time, Circadian Rhythms, and Phase Angles of Older Adults with and without Evening Naps

Parameters	With Evening Nap (n = 29)	Without Evening Nap (n = 27)	*P*-value
	Mean ± Standard Deviation		
Sleep onset time	10:37 p.m. ± 1:23	11:04 p.m. ± 1:12	.200
Sleep offset time	6:04 a.m. ± 1:06	7:02 a.m. ± 0:54	.001
aMT6s onset	9:32 p.m. ± 2:05	10:33 p.m. ± 2:17	.093
aMT6s acrophase	02:28 ± 1:21	03:38 ± 1:48	.009
aMT6s offset	7:41 ± 1:27	8:30 ± 1:58	.083
aMT6s onset to sleep onset	1.08 ± 2.10	0.53 ± 2.20	.343
Sleep onset to aMT6s acrophase	3.85 ± 1.78	4.55 ± 1.49	.116
aMT6s acrophase to sleep offset	3.60 ± 1.47	3.40 ± 1.22	.584
Sleep offset to aMT6s offset	1.61 ± 1.34	1.47 ± 1.50	.703
Cortisol acrophase	08:14 ± 1:26	08:43 ± 1:21	.199
Sleep onset to cortisol acrophase	9.61 ± 1.58	9.64 ± 1.38	.939
Sleep offset to cortisol acrophase	2.16 ± 1.25	1.69 ± 1.22	.159

aMT6s = 6-sulphatoxymelatonin.

acrophase or offset than between sleep onset time and aMT6s acrophase or onset, but the contrast between correlations was not significant (Table 5). Similar results were observed with young and older ages combined. The in-laboratory acrophases of aMT6s and cortisol were also correlated, but no correlation was observed between home TST or WASO and the amplitude of aMT6s or cortisol excretion in either age group. The mesor of aMT6s showed no correlation with TST or WASO in either age group.

DISCUSSION

In this sample of older adults, the acrophase of melatonin excretion was advanced by 37 minutes compared with that of young adults, which was less than half the 90-minute advance of the cortisol excretion acrophase and the 99-minute advance of the sleep offset. These results support previous findings of advanced circadian rhythms in aging samples.[20,21] The finding that the acrophase of melatonin excretion in older subjects was delayed in reference to the acrophase of cortisol excretion could be explained as follows. First, aMT6s acrophase might be relatively delayed because of the delayed aMT6s offset, which reflects the increase of aMT6s duration in older adults. Interesting results in Table 3 suggest that, although the onset of aMT6s had a similar relationship to sleep and cortisol in young and older adults, the offset of aMT6s (and consequently, the acrophase) was delayed in the older subjects in reference to sleep and cortisol. Two studies had similar observations with blood melatonin in aging samples.[9,22] Both this study's measure of aMT6s offset and the two studies'

Table 5. Correlations Between the Sleep-Wake Cycle and Circadian Rhythms in Young and Older Adults

Parameter	Young (n = 67)	Older (n = 56)
	Correlation Coefficient (95% Confidence Interval)	
Sleep onset—aMT6s acrophase	0.423† (0.213–0.596)	0.402* (0.145–0.608)
Sleep offset—aMT6s acrophase	0.608† (0.439–0.827)	0.602† (0.394–0.751)
Sleep onset—aMT6s onset	0.391* (0.176–0.570)	0.362* (0.099–0.578)
Sleep offset—aMT6s offset	0.529† (0.340–0.677)	0.597† (0.387–0.748)
Sleep onset—cortisol acrophase	0.532†	0.416*
Sleep offset—cortisol acrophase	0.582†	0.526†
aMT6s acrophase—cortisol acrophase	0.636†	0.619†
TST—Log_{10}aMT6s amplitude	0.181	0.043
WASO—Log_{10}aMT6s amplitude	0.071	−0.047
TST—cortisol amplitude	0.197	−0.032
WASO—cortisol amplitude	0.214	0.006

Note: 95% confidence intervals demonstrate that correlations between 6-sulphatoxymelatonin (aMT6s) circadian rhythms and sleep offset times are not different from those between aMT6s circadian rhythms and sleep onset times.

* $P < .01$, † $P < .001$.

TST = total sleep time; WASO = wake time after sleep onset.

measures of melatonin[9,22] offset reflected the declining phase after the synthesis offset (SynOff).[23] This may imply that, because of metabolic delays in older subjects, melatonin can still be detected longer after the neuronal firing of the suprachiasmatic nucleus (SCN) commences its morning increase than it can in young people. The increase of SCN neuronal firing in the morning causes consequent waking and the suppression of pineal synthesis of melatonin through N-acetyltransferase sequestration. Nevertheless, although pineal synthesis of melatonin may cease at the SynOff, declining melatonin and even aMT6s may still occupy melatonin receptors, including those in the SCN. The relatively high correlations of aMT6s offset and sleep offset support this possibility (Table 5). The relative delay of OBT in the present study may result from melatonin's influence on body temperature.[24] The functional implications of a delay between offset of pineal melatonin synthesis and offset of receptor occupancy needs much more study. Second, earlier sleep-offset time by 99 minutes in older adults might influence the large advance of cortisol acrophase. It has been reported that sleep has an inhibitory effect on cortisol levels and that awakening elevates cortisol levels.[25,26] Morning cortisol elevation might be locked to awakening in the morning, so a large phase-advance of cortisol rhythm in older adults might result from earlier wake-up time. However, in the present study, the difference in the acrophase of cortisol excretion between older adults who did and did not take evening naps was not significant, despite a 58-minute difference in sleep-offset time between these two groups of older adults. Despite the difference in the extent of phase advance, young and older adults showed high correlations between the acrophases of melatonin and cortisol excretion, as reported elsewhere.[27]

Earlier bedtimes and wake-up times and frequent awakenings during sleep characterize nocturnal sleep patterns of older adults.[28] Frequent awakenings could be described as less-consolidated sleep.[29] In the present study, the onset, acrophase, and offset of aMT6s and acrophase of cortisol showed modest correlations with sleep times. Therefore, advance of sleep times in older adults might be explained in relation to phase advances of endogenous circadian rhythms, but any causal relationship is not at all clear. Age-related amplitude reduction of circadian rhythms has been reported in several studies.[30–32] One study showed a possible involvement of amplitude reduction in the increase of wakefulness during sleep in older adults,[33] but in another study, the amplitude and mean of melatonin excretion were not related to sleep in older adults.[34] Amplitudes of melatonin and cortisol excretion in older adults were also smaller in the present study than those of young adults, but there was no correlation between amplitudes of cortisol and melatonin excretion and home sleep parameters. The mesor of aMT6s showed no correlation with TST or WASO in either age group, which is consistent with other reports that the amount of melatonin excreted is not a factor in sleep disturbance.[34,35]

To find clues about why sleep times were advanced in older adults, we explored the relationships between sleep times and circadian rhythms. Laboratory sleep propensity was advanced to the same extent as sleep times, which is expected, in that sleep propensity measures circadian modulation of sleep. That the onset of aMT6s was advanced to the same extent as sleep onset suggested a possible causal role of circadian system advance in earlier sleep onset in older people. Alternatively, sleep offset was far more advanced than the acrophase and offset of aMT6s, which implied a relative phase delay of the aMT6s circadian rhythm in reference to earlier wake-up time in older adults. Relative phase delay of circadian rhythms was supported by less advanced OBT than sleep times. Thus, a phase advance of melatonin excretion or OBT could not explain early awakening in older adults. An advance of illumination acrophase was also observed in older adults. An earlier rhythm of light exposure, by advancing endogenous circadian rhythms, could tend to produce earlier sleep times, but conversely, earlier bedtimes and arising times could produce an earlier pattern of illumination exposure. The fact that sleep was advanced more than illumination in the older group points toward the latter explanation.

In older adults, evening naps increase,[10–12] which might be a manifestation of advanced circadian rhythms. This is partly supported by the finding that older adults with evening naps showed a more advanced acrophase of melatonin excretion than those without evening naps. The onset and offset of aMT6s were also advanced in older adults who took evening naps compared with those who did not take evening naps, although the advances were statistically equivocal. However, for older subjects who took evening naps, the onset of aMT6s and acrophases of aMT6s and cortisol appeared no earlier (in reference to sleep onset) than in older subjects who did not take evening naps. In addition, there was no correlation observed between length of evening naps and the phase angle of aMT6s onset to sleep onset. Therefore, a relative advance of the circadian system in reference to sleep could not explain evening napping. If the melatonin rhythm was not advanced in reference to sleep onset in older subjects who took evening naps, there is no basis for supposing that the "sleep gate"[15] would be advanced in reference to sleep onset in these older people. Conversely, evening naps in older adults may be a factor in causing phase advance of their circadian systems, particularly by promoting early awakening and consequent earlier illumination exposure. A causal relationship between evening naps and circadian rhythms was described in a study that found that a prolonged evening nap taken from 7:00 p.m. to 1:00 a.m. in darkness resulted in a phase advance of circadian rhythms.[36]

Limitations of this study are modest inaccuracies and biases in the scoring of the sleep-wake state measured by actigraphy. Periods of wakefulness without gross movements could be mistakenly scored as sleep, but the Actillume wrist-activity monitors used in this study were reported to have 85% to 91% agreements and 0.90 to 0.98 correlations with polysomnogram.[18] Manual editing based on sleep diary and illumination data was expected to increase the accuracy of 24-hour sleep-wake scoring. The main advantage of estimating sleep using actigraphy is the feasibility of obtaining multiday 24-hour recordings in the home setting, which is practically impossible to perform using polysomnography. It is true that rectal temperature is more accurate than OBT in estimating core body temperature, but rectal probes are burdensome to subjects and have side effects such as rectal infection. OBT could

give us valuable information about circadian rhythms if carefully measured and used with other circadian makers as in this study.

In conclusion, measuring different circadian markers suggested somewhat different phase relationships between the sleep-wake cycle and endogenous circadian rhythms in aging. Early bedtime might be related to the advanced onset of the melatonin rhythm, but the advanced acrophase or offset of the melatonin rhythm could not entirely explain early awakening in older adults. Evening napping and advanced illumination might play a role in the advance of sleep-offset time and thus the circadian system in aging. Besides phase-delaying effects of evening light exposure, light-maintaining evening alertness might have potential in treating advanced sleep in aging adults.

REFERENCES

1. Weitzman ED, Moline ML, Czeisler CA et al. Chronobiology of aging: Temperature, sleep-wake rhythms and entrainment. Neurobiol Aging 1982;3: 299–309.
2. Bliwise DL. Normal aging. In: Kryger MH, Roth T, Dement WC, eds. Principles and Practice of Sleep Medicine, 3rd Ed. Philadelphia, PA: W.B. Saunders Company, 2000, pp. 26–42.
3. Richardson GS, Carskadon MA, Orav EJ. Circadian variation of sleep tendency in elderly and young adult subjects. Sleep 1982;5:S82–S94.
4. Duffy JF, Dijk DJ, Klerman EB et al. Later endogenous circadian temperature nadir relative to an earlier wake time in older people. Am J Physiol 1998; 275:R1478–R1487.
5. Monk TH, Buysse DJ, Reynolds CF et al. Circadian temperature rhythms of older people. Exp Gerontol 1995;30:455–474.
6. Youngstedt SD, Kripke DF, Elliott JA et al. Circadian abnormalities in older adults. J Pineal Res 2001;3:264–272.
7. Czeisler CA, Dumont M, Duffy JF et al. Association of sleep-wake habits in older people with changes in output of circadian pacemaker. Lancet 1992; 340:933–936.
8. Carrier J, Monk TH, Reynolds CF et al. Are age differences in sleep due to phase differences in the output of the circadian timing system? Chronobiol Int 1999;16:79–91.
9. Duffy JF, Zeitzer JM, Rimmer DW et al. Peak of circadian melatonin rhythm occurs later within the sleep of older subjects. Am J Physiol Endocrinol Metab 2002;282:E297–E303.
10. Jean-Louis G, Kripke DF, Assmus JD et al. Sleep-wake patterns among postmenopausal women: A 24-hour unattended polysomnographic study. J Gerontol A Biol Sci Med Sci 2000;55A:M120–M123.
11. Monk TH, Buysse DJ, Carrier J et al. Effects of afternoon 'siesta' nap on sleep, alertness, performance, and circadian rhythms in the elderly. Sleep 2001;24:680–687.
12. Yoon IY, Kripke DF, Youngstedt SD et al. Evening naps of older people in relation with early morning awakening [abstract]. Sleep 2002;25:A58–A59.
13. Czeisler CA, Klerman EB. Circadian and sleep-dependent regulation of hormone release in humans. Recent Prog Horm Res 1999;54:97–132.
14. Carskadon MA, Dement WC. Sleep studies on a 90-minute day. Electroencephalogr Clin Neurophysiol 1975;39:145–155.
15. Lavie P. Ultrashort sleep-waking schedule. III. 'Gates' and 'forbidden zones' for sleep. Electroencephalogr Clin Neurophysiol 1986;63:414–425.
16. Buysse DJ, Reynolds CF, Monk TH et al. The Pittsburgh Sleep Quality Index. New instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.
17. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. Appl Psychol Measure 1977;1:385–401.
18. Jean-Louis G, Kripke DF, Cole RJ et al. Sleep detection with an accelerometer actigraph: Comparisons with polysomnography. Physiol Behav 2001;72: 21–28.
19. Jean-Louis G, Kripke DF, Ancoli-Israel S et al. Circadian sleep, illumination, and activity patterns in women: Influences of aging and time reference. Physiol Behav 2000;68:347–352.
20. Van Coevorden A, Mockel J, Laurent E et al. Neuroendocrine rhythms and sleep in aging men. Am J Physiol 1991;260:E651–E661.
21. Van Cauter E, Leproult R, Kupfer DJ. Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. J Clin Endocrinol Metab 1996; 81:2468–2473.
22. Reid KJ, Baehr EK, Vaidya P et al. Relationship between sleep times and melatonin rhythm in older and young adults [abstract]. SRBR 2002;8:A58.
23. Lewy AJ, Cutler NL, Sack RL. The endogenous melatonin profile as a marker for circadian phase position. J Biol Rhythms 1999;14:227–236.
24. Cagnacci A, Elliott JA, Yen SS. Melatonin. A major regulator of the circadian rhythm of core temperature in humans. J Clin Endocrinol Metab 1992; 75:447–452.
25. Weitzman ED, Zimmerman JC, Czeisler CA et al. Cortisol secretion is inhibited during sleep in normal man. J Clin Endocrinol Metab 1983;56:352–358.
26. Weibel L, Follenius M, Spiegel K et al. Comparative effect of night and daytime sleep on the 24-hour cortisol secretory profile. Sleep 1995;18:549–556.
27. Skene DJ, Lockley SW, James K et al. Correlation between urinary cortisol and 6-sulphatoxymelatonin rhythms in field studies of blind subjects. Clin Endocrinol 1999;50:715–719.
28. Dijk DJ, Duffy JF, Czeisler CA. Age-related increase in awakenings. Impaired consolidation of NREM sleep at all circadian phases. Sleep 2001;24:565–577.
29. Dijk DJ, Duffy JF, Riel E et al. Ageing and the circadian and homeostatic regulation of human sleep during forced desynchrony of rest, melatonin and temperature rhythms. J Physiol (Lond) 1999;516:611–627.
30. Touitou Y. Effects of aging on endocrine and neuroendocrine rhythms in humans. Horm Res 1995;43:12–19.
31. Van Cauter E, Plat L, Leproult R et al. Alterations of circadian rhythmicity and sleep in aging: endocrine consequences. Horm Res 1998;49:147–152.
32. Dijk DJ, Duffy JF, Czeisler CA. Contribution of circadian physiology and sleep homeostasis to age-related changes in human sleep. Chronobiol Int 2000;17:285–311.
33. Carrier J, Monk TH, Buysse DJ et al. Amplitude reduction of the circadian temperature and sleep rhythms in the elderly. Chronobiol Int 1996;13:373–386.
34. Youngstedt SD, Kripke DF, Elliott JA. Melatonin excretion is not related to sleep in the elderly. J Pineal Res 1998;24:142–145.
35. Lushington K, Lack L, Kennaway DJ et al. 6-Sulfatoxymelatonin excretion and self-reported sleep in good sleeping controls and 55–80-year-old insomniacs. J Sleep Res 1998;7:75–83.
36. Buxton OM, L'Hermite-Baleriaux M, Turek FW et al. Daytime naps in darkness phase shift the human circadian rhythms of melatonin and thyrotropin secretion. Am J Physiol Regul Integr Comp Physiol 2000;278: R373–R382.