Age-Related Changes in Slow Wave Sleep and REM Sleep and Relationship With Growth Hormone and Cortisol Levels in Healthy Men

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Decreased subjective sleep quality is one of the most common health complaints of older adults. The most consistent alterations associated with normal aging include increased number and duration of awakenings and decreased amounts of deep slow wave (SW) sleep (ie, stages 3 and 4 of non-rapid eye movement (non-REM) sleep). REM sleep appears to be relatively better preserved during aging. The age at which changes in amount and distribution of sleep stages appear is unclear because the majority of studies have been based on comparisons of young vs older adults. Several investigators have noticed that there are marked decreases in SW sleep in early adulthood in men but not in women.

Sleep is a major modulator of endocrine function, particularly of pituitary-dependent hormonal release. Growth hormone (GH) secretion is stimulated during sleep and, in men, 60% to 70% of daily GH secretion occurs during early sleep, in association with SW sleep. Whether decrements in SW sleep contribute to the well-known decrease in GH secretion in normal aging is not known.

Context In young adults, sleep affects the regulation of growth hormone (GH) and cortisol. The relationship between decreased sleep quality in older adults and age-related changes in the regulation of GH and cortisol is unknown.

Objective To determine the chronology of age-related changes in sleep duration and quality (sleep stages) in healthy men and whether concomitant alterations occur in GH and cortisol levels.

Design and Setting Data combined from a series of studies conducted between 1985 and 1999 at 4 laboratories.

Subjects A total of 149 healthy men, aged 16 to 83 years, with a mean (SD) body mass index of 24.1 (2.3) kg/m², without sleep complaints or histories of endocrine, psychiatric, or sleep disorders.

Main Outcome Measures Twenty-four-hour profiles of plasma GH and cortisol levels and polygraphic sleep recordings.

Results The mean (SEM) percentage of deep slow wave sleep decreased from 18.9% (1.3%) during early adulthood (age 16-25 years) to 3.4% (1.0%) during midlife (age 36-50 years) and was replaced by lighter sleep (stages 1 and 2) without significant increases in sleep fragmentation or decreases in rapid eye movement (REM) sleep. The transition from midlife to late life (age 71-83 years) involved no further significant decrease in slow wave sleep but an increase in time awake of 28 minutes per decade at the expense of decreases in both light non-REM sleep (−24 minutes per decade; P<.001) and REM sleep (−10 minutes per decade; P<.001). The decline in slow wave sleep from early adulthood to midlife was paralleled by a major decline in GH secretion (−372 µg per decade; P<.001). From midlife to late life, GH secretion further declined at a slower rate (−43 µg per decade; P<.02). Independently of age, the amount of GH secretion was significantly associated with slow wave sleep (P<.001). Increasing age was associated with an elevation of evening cortisol levels (+19.3 nmol/L per decade; P<.001) that became significant only after age 50 years, when sleep became more fragmented and REM sleep declined. A trend for an association between lower amounts of REM sleep and higher evening cortisol concentrations independent of age was detected (P<.10).

Conclusions In men, age-related changes in slow wave sleep and REM sleep occur with markedly different chronologies and are each associated with specific hormonal alterations. Future studies should evaluate whether strategies to enhance sleep quality may have beneficial hormonal effects.

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sleep. Furthermore, even partial sleep deprivation results in an elevation of cortisol levels the following evening. Thus, both decreased SW sleep and sleep loss resulting from increased sleep fragmentation could contribute to elevating cortisol levels. An elevation of evening cortisol levels is a hallmark of aging and cortisol levels in healthy men and examinees whether decrements in sleep quality are associated with alterations of GH and cortisol levels.

**METHODS**

**Subjects**

Data from a total of 149 healthy men, aged 16 to 83 years, are presented. Mean (SD) body mass index (BMI) of the subjects was 24.1 (2.3) kg/m². All subjects were of normal weight (BMI, 18-28 kg/m²). The subjects were paid volunteers, and cortisol, and cortisol levels in healthy men and examinees whether decrements in sleep quality are associated with alterations of GH and cortisol levels.

The present study defines the chronology of age-related changes in sleep duration and quality (ie, amounts of sleep stages), GH secretion, and cortisol levels in healthy men and examinees whether decrements in sleep quality are associated with alterations of GH and cortisol levels.

**Methods**

**Subjects**

Data from a total of 149 healthy men, aged 16 to 83 years, are presented. Mean (SD) body mass index (BMI) of the subjects was 24.1 (2.3) kg/m². All subjects were of normal weight (BMI, 18-28 kg/m²). The data were collected between 1985 and 1999 in a series of studies from our group (109 out of 149 individual data sets) and 3 other laboratories using similar assay procedures, recording procedures, or both (University of Pittsburgh, Pittsburgh, Pa, 14 subjects; University of California, Los Angeles, 8 subjects; and Pennsylvania State University, Hershey, 18 subjects). Except for data from 29 subjects studied in our laboratory, all other data were included in previously published reports that did not address the chronology of age effects. The raw data from all 149 subjects were submitted to a new analysis designed to quantitatively define sleep and hormonal parameters across adulthood.

The subjects were paid volunteers who had no sleep complaints, did not take any drugs, were in good health based on a physical examination, and had no history of endocrine, psychiatric, or sleep disorders. Shift workers, subjects recently having traveled across time zones, and competitive athletes were excluded in previous studies.

**Experimental Protocol**

Prior to the study, the subjects spent 1 to 3 habituation nights in the sleep laboratory. In studies including hormonal measurements (133 of 149 studies), a catheter was inserted into a forearm vein and blood samples were collected at 15- to 30-minute intervals for 24 to 25 hours. During the night, the catheter was connected to tubing extending to an adjacent room to avoid disturbing the subject. All-night polygraphic sleep recordings were obtained. The subjects remained recumbent in bed in darkness for at least 8 hours. Daytime naps were not allowed.

Sleep, cortisol, and GH profiles were obtained in 132, 124, and 114 subjects, respectively. Concomitant sleep, cortisol, and GH profiles were obtained in 94 subjects.

**Sleep Recording and Analysis**

Polygraphic sleep recordings were visually scored at 20- or 30-second intervals in stages wake, 1, 2, 3, and 4, and REM using standardized criteria. Sleep onset and morning awakening were defined, respectively, as the times of occurrence of the first and last interval scored as stage 2, 3, 4, or REM. The sleep period was defined as the interval separating sleep onset from morning awakening. The total sleep time was calculated as the sleep period minus the total duration of awakenings. The total duration of each stage was expressed in minutes as well as a percentage of the sleep period. Slow wave sleep was defined as the sum of stages 3 and 4.

**Hormonal Assays**

In all studies, cortisol levels were measured by a standard radioimmunoassay (RIA). The limit of sensitivity averaged 27.6 nmol/L and intra-assay coefficients of variation (CV) were 5% to 10%.

In 89 profiles, GH concentrations were measured by an RIA with a sensitivity of 0.4 µg/L. Intra-assay CV ranged from 5% to 9%. The interassay CV averaged 15%. In 25 studies, GH concentrations were measured by a chemiluminescence method (8 studies: Nichols Institute Diagnostics, San Juan Capistrano, Calif; and 17 studies: Diagnostic Product Corporation, Los Angeles, Calif) with a limit of sensitivity of 0.002 to 0.003 µg/L, an intra-assay CV ranging from 4.8% to 9.9%, and an interassay CV less than 8%. Baseline, ie, nonpulsatile, concentrations of GH less than 1 µg/L by chemiluminescence correspond to concentrations less than the limit of sensitivity (0.4 µg/L) by RIA. Estimations of pulsatile GH secretion greater than baseline levels derived from GH profiles measured by chemiluminescence do not differ significantly from those measured by RIA.

**Analysis of Individual Cortisol Profiles**

The circadian variation of plasma cortisol was quantified using a best-fit curve based on periodogram calculations. The acrophase and nadir were defined, respectively, as the times of occurrence of the maximum and minimum of the best-fit curve. The value of the acrophase or nadir was defined as the level attained by the best-fit curve at the acrophase or nadir.

**Analysis of Individual GH Profiles**

Significant pulses of GH secretion greater than baseline levels were identified using a computerized algorithm. The threshold for significance was set at 2 times the intra-assay CV. For each significant pulse, the amount of GH secreted above baseline level was estimated by mathematical deconvolution based on a 1-compartment model for GH clearance and variable individual half-lives. The total amount of GH secreted over a given time interval was determined by summing the amounts secreted in each of the pulses occurring during that time interval.
Statistical Analysis
Each of the parameters used to quantify sleep, GH secretion, and the 24-hour cortisol profile was used in 2 analyses. First, the parameter was considered as a dependent variable in an analysis of variance (ANOVA) including age, BMI, and the interaction age × BMI as independent variables. When the interaction age × BMI had \( P > .05 \) based on type III sums of squares, the analysis was repeated with only age and BMI as independent variables. To verify that significant interactions did not reflect the impact of a single subject, the calculations were repeated after excluding data from the most outlying subject for the variables in the analysis. The interaction was maintained in the analysis only if the statistical significance was not critically dependent on a single subject. Second, the data were grouped by age ranges (aged 16-25 years, 42 subjects; aged 26-35 years, 28 subjects; aged 36-50 years: 26 subjects; aged 51-60 years, 23 subjects; aged 61-70 years, 18 subjects; and aged 71-83 years, 12 subjects). For each parameter, simple linear regressions with age as an independent variable were calculated separately for subjects from early adulthood (aged 16-25 years) to 43 years, ie, the midpoint of the midlife range (aged 36-50 years), and for subjects from midlife to late life (aged 44-83 years). Unless otherwise indicated, all group values are expressed as mean (SEM).

RESULTS
Sleep
Consistent with previous reports,\(^3\)\(^-\)\(^5\) the sleep period was not significantly affected by age. In contrast, total sleep time decreased markedly with aging (\( P < .001 \)), but significant reductions in total sleep time did not occur until after midlife. From midlife until the eighth decade, total sleep time decreased, on average, by 27 minute per decade (TABLE, next page).

Aging had a differential impact on sleep parameters (FIGURE 1). From early adulthood to midlife (age 16-25 to 36-50 years), the percentage of SW sleep decreased from 18.9% (1.3%) to 3.4% (1.0%), and this decrease in deep non-REM sleep was compensated by an increase in light non-REM sleep (ie, stages 1 and 2) from 51.2% (1.4%) to 67.3% (1.6%) without significant change in time spent awake. There were no changes in REM sleep from early...
adulthood to midlife. Increases in wake time and decreases in REM sleep became significant starting at midlife, and stages 1 and 2 decreased from 60.5% (2.5%) for subjects aged 51 to 60 years to 50.6% (4.6%) for subjects older than 70 years. Changes in SW sleep after age 50 years were not significant.

Effects of BMI and of the interaction age × BMI were significant for stages 1 and 2 and SW sleep, but not for other sleep parameters (Figure 1). In young to middle-aged subjects (aged 16–43 years), but not in older adults (aged 44–83 years), higher BMI was associated with shallower, non-REM sleep (less SW sleep, more stages 1 and 2 sleep).

Growth Hormone
Mean 24-hour GH profiles from 8 older men and 8 young men who were matched for BMI illustrate the temporal coincidence of the major GH pulse with early sleep and the marked reduction in GH levels in old age (Figure 2). The impact of age on GH secretion during the 24-hour cycle, wake time, and sleep, is illustrated in Figure 3. Significant effects of age independent of BMI were evident. From young adulthood to midlife, GH secretion decreased by nearly 75%. Further smaller decreases occurred between midlife and late adulthood (Table). A significant negative association of BMI with 24-hour GH secretion and GH secretion during waking, but not during sleep, was detected independently of age.

Cortisol
Mean 24-hour cortisol profiles in young and older men are shown in the lower panels of Figure 2. In both groups, cortisol levels show an early morning elevation, declining levels throughout the daytime, and a nocturnal quiescent period. Age differences are mostly apparent in the evening and early part of the night.

Figure 4 illustrates the changes in 24-hour mean cortisol level, morning acrophase, and evening nadir across adulthood. A modest effect of aging on the 24-hour mean cortisol level was detected. Aging was associated with an el-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early Adulthood to Midlife (Age 16 to 43 Years)†</th>
<th>P Value</th>
<th>Midlife to Late Life (Age 44 to 83 Years)‡</th>
<th>P Value</th>
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<td>.69</td>
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<td>−10</td>
<td>&lt;.001</td>
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<td>−38</td>
<td>&lt;.001</td>
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<td>.13</td>
</tr>
<tr>
<td>Stages 1 and 2</td>
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<td>&lt;.001</td>
<td>−24</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Growth Hormone, µg/decade

| 24-Hour GH secretion          | −372                                            | <.001     | −43                                      | <.02      |
| Waking GH secretion           | −150                                            | .002      | −27                                      | .05       |
| Sleeping GH secretion         | −221                                            | <.001     | −16                                      | <.06      |

Cortisol, nmol/L per decade

| 24-Hour mean level            | +0.6                                            | .99       | +11.0                                    | <.07      |
| Morning acrophase level       | −8.8                                            | .66       | +10.2                                    | .32       |
| Evening nadir level           | −1.7                                            | .81       | +19.3                                    | <.001     |

*REM indicates rapid eye movement; SW, slow wave; and GH, growth hormone.
†Data from 74 men was analyzed for “Sleep,” from 66 for “Growth Hormone,” and from 71 for “Cortisol.”
‡Data from 58 men was analyzed for “Sleep,” from 48 for “Growth Hormone,” and from 53 for “Cortisol.”
§Sleep period was defined as the interval separating sleep onset from morning awakening. Total sleep time was calculated as the sleep period minus the total duration of awakenings.
| To convert nmol/L to ng/mL, divide by 2.759.

Figure 2. Mean 24-Hour Profiles of Plasma Growth Hormone (GH) and Plasma Cortisol From Young and Older Men Matched for BMI

BM indicates body mass index. The mean (SD) BMI in the older men was 24.1 (0.8) kg/m² and in young men, 24.1 (0.6) kg/m². Dashed line indicates SEM.
evation of the evening nadir, but morning maximum values remained stable across all age ranges. Increases in evening cortisol levels became apparent after midlife (Table).

There were no effects of BMI or of the interaction BMI $\times$ age on any of the parameters characterizing the 24-hour cortisol profile.

**Relationships Between Sleep and Hormonal Alterations**

Age-related decreases in GH secretion and SW sleep followed a similar chronology, with the majority of the decrements occurring in young adulthood, whereas age-related increases in evening cortisol did not occur until the fifth decade, when decreases in REM sleep and increases in amount of wake time became apparent (Table). We thus sought to determine whether the concomitant sleep alteration and its interaction with age contributed to the hormonal changes.

Analysis of variance of GH secretion during sleep in relation to age, SW sleep, and their interaction indicated that SW sleep ($P<.001$) and the interaction age $\times$ SW sleep ($P=.008$) accounted for the majority of the variance and that effects of age per se were nonsignificant ($P>.50$). Similar findings were obtained when total 24-hour GH secretion was analyzed (age, $P>.50$; SW sleep, $<.001$; age $\times$ SW sleep, $P=.003$). In young to middle-aged subjects, but not in older men, increased amounts of SW sleep were associated with higher levels of GH secretion. The left panels of Figure 5 compare GH levels during sleep in subjects who had large amounts of SW sleep and in age- and BMI-matched subjects who had small amounts of SW sleep.

The variance of evening cortisol levels was analyzed in relation to age, REM sleep, wake time, and their interactions. The contributions of all interactions and of wake time were not significant. Age ($P<.001$) and, to a lesser extent, REM sleep ($P<.10$) were both negatively related to evening cortisol concentrations. To illustrate the inverse relationship between amounts of REM sleep and evening cortisol levels, the right panels of Figure 5 show the mean cortisol nadir in subjects with large amounts of REM sleep and in age- and BMI-matched subjects with small amounts of REM sleep.

**COMMENT**

The present analysis demonstrates that, in healthy men, aging affects SW sleep and GH release with a similar chronology characterized by major decrements from early adulthood to midlife. In contrast, the impact of age on REM sleep, sleep fragmentation, and HPA function does not become apparent until later in life. The analysis further suggests that age-related alterations in the somatotropic and corticotropic axes may partially reflect decreased sleep quality.

Human sleep is under the dual control of circadian rhythmicity and of a homeostatic process relating the depth of sleep to the duration of prior wakefulness. This homeostatic process involves a putative neural sleep factor that increases during waking and decays ex-
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Figure 4. 24-Hour Mean Level and Levels of Morning Acrophase and Evening Nadir of Plasma Cortisol as a Function of Age

Mean (SEM) for each age group shown in the left panels. Individual data are plotted in the right panels. BMI indicates body mass index. Probability levels refer to the effect of age, BMI, and their interaction in an analysis of variance (ANOVA) model using type III sums of squares. When level of interaction was not significant (P > .05), the interaction was removed from the ANOVA. P values for age and BMI are then reported for ANOVA without interaction. The multiple correlations were r = 0.243 for 24-hour mean level, r = 0.089 for level of morning acrophase, and r = 0.244 for level of evening nadir.

Potentially during sleep. Slow wave sleep is primarily controlled by the homeostatic process. Circadian rhythmicity is an oscillation with a near 24-hour period generated by a pacemaker located in the hypothalamic suprachiasmatic nucleus. Circadian rhythmicity plays an important role in sleep timing, sleep consolidation, and the distribution of REM sleep. The present data indicate that an alteration in sleep-wake homeostasis is an early biological marker of aging in adult men. In contrast, components of sleep that are under the control of the circadian pacemaker appear to be relatively well preserved until late in life.

The chronology of aging of GH secretion follows a pattern remarkably similar to that of SW sleep. Thus, in men, the so-called “somatopause” occurs early in adulthood, between age 25 and 35 years, an age range that corresponds to the human life expectancy before the development of modern civilization and is essentially completed by the end of the fourth decade. Our analyses further indicate that reduced amounts of SW sleep, independent of age, are partly responsible for reduced GH secretion in midlife and late life. That this correlative evidence reflects a common mechanism underlying SW sleep generation and GH release rather than an indirect association is supported by 2 studies that have shown that pharmacological enhancement of SW sleep results in increased GH release. Also supporting a causal relationship between decreased sleep quality and reduced nocturnal GH secretion are studies in patients with sleep apnea showing a marked increase in GH release following treatment with positive airway pressure. The reverse interaction between sleep and GH, that is, a deleterious impact of reduced somatotropic function on sleep, is also possible since studies in both normal and pathological conditions have shown that GH-releasing factor and GH influence sleep quality.

In the present study of nonobese men, the finding of a negative impact of BMI on both GH secretion during waking and amount of SW sleep is consistent with the hypothesis that inhibition of the GH axis may adversely affect sleep regulation.

While the clinical implications of decreased SW sleep are still unclear, the relative GH deficiency of the elderly is associated with increased fat tissue and abdominal obesity, reduced muscle mass and strength, and reduced exercise capacity. Multiple trials are currently examining the clinical usefulness and safety of replacement therapy with recombinant GH, the other hormones of the GH axis, and synthetic GH secretagogues in elderly adults without pathological GH deficiency. While the benefits of such interventions are still unknown, the present findings suggest that they should target a younger age range than currently envisioned, ie, individuals in early midlife rather than those older than 65 years, when peripheral tissues have been continuously exposed to very low levels of GH for at least 2 decades. Furthermore, since pharmacological enhancement of SW sleep in young adults has been shown to result in a simultaneous and proportional increase in GH release and ongoing studies in our laboratory indicate that

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Left, direct relationship between slow wave (SW) sleep and growth hormone (GH) secretion during sleep in men who were matched for age and body mass index (BMI) but had either high amounts of SW sleep (>50th percentile of the distribution in subjects aged 16-44 years) or low amounts of SW sleep (<50th percentile of the distribution). Right, inverse relationship between rapid eye movement (REM) sleep and level of the evening cortisol nadir in men who were matched for age and BMI but had either high amounts of SW sleep (>50th percentile of the distribution in subjects aged 16-44 years) or low amounts of SW sleep (<50th percentile of the distribution).

In conclusion, in healthy men, the distinct changes in sleep quality that characterize the transitions from early adulthood to midlife, on the one hand, and from midlife to old age, on the other hand, are each associated with specific alterations in hormonal systems that are essential for metabolic regulation. Strategies to prevent or limit decrements of sleep quality in midlife and late life may therefore represent an indirect form of hormonal therapy with possible beneficial health consequences.

**REFERENCES**


**Figure 5. Hormone Secretion and Sleep Stage**

<table>
<thead>
<tr>
<th>No. of Subjects</th>
<th>GH Secretion During Sleep, µg</th>
<th>Cortisol Nadir and REM Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High SWS</td>
<td>Low SWS</td>
</tr>
<tr>
<td>Age, Mean (SD), y</td>
<td>24.7 (0.8)</td>
<td>24.5 (1)</td>
</tr>
<tr>
<td>BMI, Mean (SD), kg/m²</td>
<td>23.1 (0.5)</td>
<td>23.1 (0.5)</td>
</tr>
</tbody>
</table>

Similar effects can be obtained in older subjects, drugs that reliably stimulate SW sleep may represent a novel class of GH secretagogues.

The present data demonstrate that the amount of REM sleep is reduced by approximately 50% in late life vs young adulthood. However, reduced amounts of REM sleep and significant sleep fragmentation do not occur until after age 50 years. The impact of aging on cortisol levels followed the same chronology. Aging was associated with an elevation of evening cortisol levels, reflecting an impaired ability to achieve evening quiescence following morning stimulation. Studies in both animals and humans have indicated that deleterious effects of HPA hyperactivity are more pronounced at the time of the trough of the rhythm than at the time of the peak.

Elevated evening cortisol levels in late life probably reflect an impairment of the negative feedback control of the HPA axis in aging. Our analyses suggest that there is a relationship between this alteration of HPA function and decreased amounts of REM sleep that is independent of age. The data generally support the concept that decreased sleep quality contributes to the allostatic load, ie, the wear and tear resulting from overactivity of stress-responsive systems.

The present study focused on the effects of aging on the relationship between sleep and the somatotopic and corticotrophic axes in men because the predominant GH secretion occurs during sleep in men but not in women and because there is evidence to suggest that the marked decreases in SW sleep in early adulthood occur in men but not in women. Whether conclusions similar to those obtained for men hold for women will require a separate evaluation as sex differences in sleep quality as well as 24-hour profiles of GH and cortisol secretion have been well documented in both young and older adults.

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