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Changes in Cortisol and Growth Hormone Secretion During Nocturnal Sleep in the Course of Aging

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Background. One current hypothesis of biological aging proposes that aging results from the deterioration of neuroendocrine functions. Sleep dependent growth hormone (GH) secretion is diminished in elderly people. However, the time course of this decrease from puberty to senescence is still unknown. Cortisol secretion is also related to sleep processes with the 24 hr nadir occurring, like the sleep dependent GH secretory surge, during the first half of nocturnal sleep. Whether age also affects the sleep-associated nadir of cortisol secretion has yet to be clarified. This study investigated changes in GH and cortisol secretion during sleep in 30 male volunteers age 20 to 92 yr.

Methods. After an adaptation night, each subject spent another night in the sleep laboratory for polygraphic sleep recording and determination of GH and cortisol levels every 15 min.

Results. GH peak values exponentially decreased with age ($r = -.80$, $p < .001$), while the cortisol nadir increased linearly as a function of age ($r = .79$, $p < .001$). Age-related changes in sleep-dependent secretion of GH and cortisol correlated significantly ($r = .47$, $r = -.55$, respectively; $p < .05$) with an age-dependent decrease in slow wave sleep.

Conclusion. Alterations of GH peak amplitude and basal cortisol secretion are not restricted to senescence. These changes develop gradually during adult life with different time courses. Both changes in GH and cortisol secretion may act together to reduce anabolic functions of sleep in the aged.

IT is well established that growth hormone (GH) secretion distinctly increases during the first two NonREM/REM (rapid eye movement) sleep cycles, and these increases typically coincide with the first nocturnal episodes of slow wave sleep (1). Delaying sleep onset delays not only the onset of slow wave sleep (SWS), but also the nocturnal GH secretory burst (2), suggesting a linkage between mechanisms of GH secretion and of those initiating sleep.

Cortisol secretion is also closely linked to sleep processes such that during REM sleep the secretory activity is inhibited (3). Moreover, when GH secretion increases during the first two NonREM/REM sleep cycles, cortisol concentration reaches a 24 hr minimum (4). Several studies have indicated an inhibited pituitary-adrenal axis during this period of sleep (5).

In elderly people both a decline in time spent in SWS and a decrease of REM sleep have been reported (6,7). Moreover, nocturnal GH secretion is known to be reduced in elderly as compared to young subjects (6,8). However, results are inconsistent regarding the basal cortisol secretion in elderly people. Pavlov et al. (9) reported on elevated basal cortisol levels in elderly men awake in the evening, whereas other studies failed to find any effect of age on cortisol concentrations measured in the morning (10,11). However, in the morning, pituitary-adrenal secretion is activated due to its circadian rhythm (12). The cortisol nadir in the beginning of nocturnal sleep therefore may represent a more valid estimate of basal secretory activity of this system (13). Moreover, during sleep, assessment of basal cortisol levels is least contaminated by stress-related activity of the pituitary-adrenal axis to external stimuli.

The present study examined age-related changes from young adult life to senescence, in the GH surge and in the cortisol nadir at the beginning of nocturnal sleep. At present, little is known about the time course of these changes although this might be of considerable clinical and therapeutic relevance (14). A decrease in SWS and REM sleep in the aged, which has been well established (6,7), might be associated with age-related changes in hormone secretory activity during sleep. For these purposes, besides the cortisol and GH secretory activity, sleep parameters were measured within a wide range of age (20 to 92 yr).

Methods

Subjects were 30 healthy, nonhospitalized, fully self-sufficient men aged 20–92 yr. Subjects were not taking any medication and had no history of psychiatric disorders, sleep complaints, or signs of cognitive impairment. All subjects underwent a medical examination and routine laboratory tests. Body weight was within 15% of their ideal weight (mean weight ± *SE:* 70.4 ± 5.6 kg; height: 178.8 ± 4.8 cm). Written informed consent was obtained from all men. The study was approved by the ethics committee of the University of Lübeck.

Subjects arose before 0700 hr on the days before experimental nights, and did not take any naps during the day. They were acclimated to the experimental sleep condition by spending one night under conditions of the experiment.

The experiments took place in an air-conditioned, electrically shielded room. Upon arrival in the laboratory at 1900 hr, subjects were prepared for somnopolygraphic recording and blood sampling. Lights were turned off at 2300 hr, and

continuous recordings and blood samples were obtained until 0700 hr, when the subjects were awakened. Blood samples for determination of plasma cortisol and GH concentrations were taken every 15 min via an intravenous forearm catheter connected to a long thin tube (vol 1.5 mL). This enabled blood collection from an adjacent room without disturbing the subject's sleep.

Sleep was monitored polygraphically and scored offline independently by the same two experienced raters, who did not know the subjects' age, according to the criteria described by Rechtschaffen and Kales (15). Sleep recordings from 10 subjects were lost, so sleep was evaluated for a reduced sample of 20 subjects aged between 25–92 yr.

GH and cortisol were measured by radioimmunoassay (GH-assay: bioMerieux, Nürtingen, Germany, sensitivity: 0.5 μg/l; intraassay coefficient of variation: 5% between 1.5 and 60 μg/l; cortisol-assay: Biermann Diagnostica, Bad Nauheim, Germany, 5.5 nmol/l, 3% between 69.0 and 1380 nmol/l). The interassay coefficient was below 10% in all assays. Samples from an individual subject were analyzed in duplicate in the same assay.

For each night, total sleep time and the time (in min) spent in SWS (sleep stage 3 and 4) and REM sleep were determined. Moreover, mean GH and cortisol levels during the night, the maximum GH and cortisol concentrations, and the cortisol nadir concentration were determined, defined as the highest and lowest absolute values, respectively, during the sleep period. Latency of the GH maximum, the cortisol maximum, and cortisol nadir was calculated with reference to sleep onset, defined as the onset of the first epoch of stage 1 sleep followed by stage 2 sleep.

Statistical evaluation was based on regression analysis (BMDP 6R and AR) including linear and exponential regression functions (16). An exponential regression function was used when the variance determined exceeded that obtained by a linear regression function by more than 10%. In addition, partial correlation analyses were performed, removing the linear effects of SWS and REM sleep as independent variables to determine to what extent changes in cortisol and GH secretion with age were independent of changes in sleep. A p-value $< .05$ was considered significant.

Results

Table 1 summarizes correlation coefficients for linear or exponential relations between any two of the variables. As expected, SWS decreased with age, and this relationship was best fit by a linear regression ($r = -.56$, $p < .01$, $n = 20$). REM sleep also appeared to linearly decrease with increasing age ($r = -.55$, $p < .01$, $n = 20$; Figure 1, C and D). The decrease in SWS with increasing age was positively correlated to the maximum GH concentration ($r = .47$, $p < .05$, $n = 20$), and negatively correlated to the cortisol nadir concentration ($r = -.55$, $p < .01$, $n = 20$; Figure 1, E and F). REM sleep failed to correlate with any of the hormone parameters.

In all subjects, GH peak concentrations were reached within the first two NonREM/REM sleep cycles. Maximum GH concentrations decreased exponentially with increasing age ($r = -.80$, $p < .001$, $n = 30$; Figure 1A). Based on the respective regression function, beyond the age of 36 yr, GH peak concentrations were estimated to be lower than the mean GH peak concentration for the total subject sample, which was 5.45 μg/l.

Also, mean GH concentrations within the sleeping period decreased exponentially with increasing age (exponential regression equation: GH mean [μg/l] $= 5.4 * e^{-.03 * \text{Age (yrl)}}$; $r = -.70$, $p < .001$, $n = 30$). Removing the linear effects of SWS and REM sleep, the partial correlation between the maximum GH concentration and age significantly ($p < .05$) diminished to $r = -.33$, and failed per se to reach significance. Similarly, the correlation between mean GH levels and age decreased ($r = -.54$, $p < .01$, $n = 20$) when influences of SWS and REM sleep were removed. The latencies of GH maximum concentrations failed to correlate with any of the other parameters.

To separate effects of age on GH peak concentrations from those on the nocturnal mean GH concentrations, GH peak concentrations were expressed as the percentage of the mean GH concentration during the night. The transformed values of GH peak concentrations also decreased with age ($r = -.66$, $p < .001$, $n = 30$; Figure 2).

Like GH secretory surges, all cortisol nadirs occurred within the first two NonREM/REM sleep cycles, and none of the subjects had a phase of wakefulness longer than 2 min during the 60 min preceding the nadir. There was a substantial linear positive correlation between nadir concentrations of cortisol and age, indicating increasing nadirs with increasing age ($r = .79$, $p < .001$, $n = 30$; Figure 1B). In contrast to GH peak concentrations, the partial correlation between cortisol nadir concentrations and age after removing the linear effects of SWS and REM sleep remained almost unchanged ($r = .72$, $p < .001$, $n = 20$). Cortisol nadirs

Table 1. Correlation Matrix of Measured Variables

	Age	SWS	REM	GH mean	GH max	Cort mean
SWS	–0.56**					
REM	–0.55**	0.13				
GH mean	–0.70***	0.33	0.36			
GH max	–0.80***	0.47*	0.31	0.67***		
Cort mean	0.61**	–0.29	–0.32	–0.45*	–0.48**	
Cort nadir	0.79***	–0.55**	–0.26	–0.43*	–0.62**	0.54**

Note: Correlation coefficients for the linear relations (exponential relations underlined) between any two of the variables (age 25–92 yr, $n = 20$), time spent in slow wave sleep (SWS) and rapid eye movement (REM) sleep, mean GH levels (GH mean) and maximum GH concentrations (GH max), mean cortisol levels (Cort mean), and the cortisol nadir concentration (Cort nadir) during the night.

*$p < .05$; **$p < .01$; ***$p < .001$.

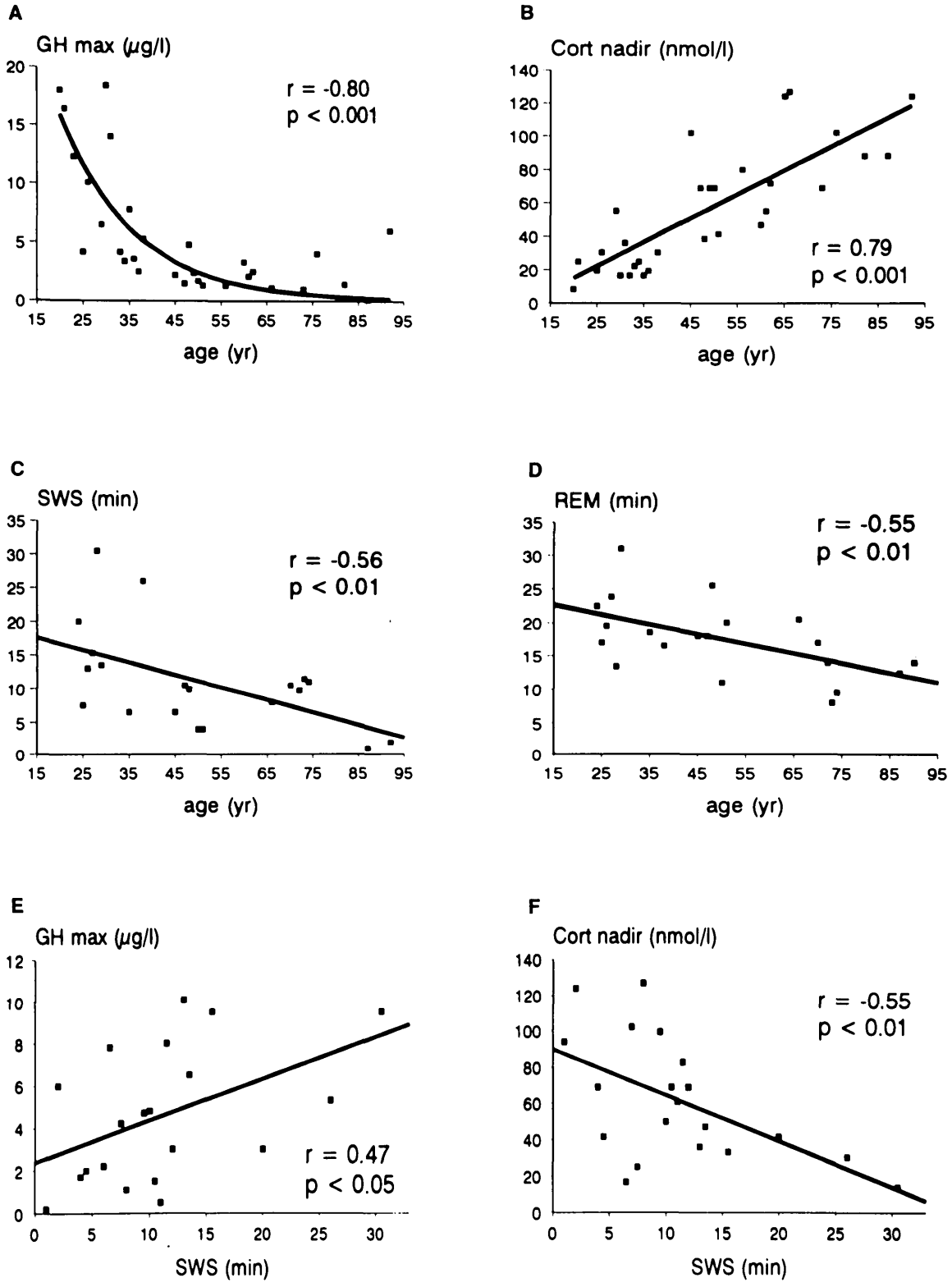

Figure 1. The relationships are as follows: **A** between maximum growth hormone (GH) concentrations during sleep and age (exponential regression equation: GH max [μg/l] = 55.5 * $e^{-.06 * \text{Age [yr]}}$; n = 30); **B** between the cortisol nadir during sleep and age (linear regression equation: Cort nadir [nmol/l] = 1.44 * Age [yr] −13.8; n = 30); **C** between time spent in SWS (in min) and age (yr) (linear regression equation: SWS [min] = −.18 * Age [yr] + 20.3; n = 20); **D** between time spent in REM sleep (in min) and age (yr) (linear regression equation: REM [min] = −.15 * Age [yr] + 24.8; n = 20); **E** between maximum GH concentrations and the time spent in SWS (linear regression equation: GH max [μg/l] = .20 * SWS [min] + 2.39; n = 20); and **F** between the cortisol nadir during sleep and the time spent in SWS (linear regression equation: Cort nadir [nmol/l] = −2.53 * SWS [min] + 89.8; n = 20). Correlation coefficients and their significance are indicated. To convert plasma concentrations of GH to ng/ml and of cortisol to μg/dl, multiply by 1.0 and 27.59, respectively.

exceeding the mean of all subjects (56.3 nmol/l) were estimated to occur beyond the age of 47 yr.

Similar to the cortisol nadir concentrations, the mean cortisol concentrations during the whole night increased linearly with age (linear regression equation: Cort mean [nmol/l] = 2.06 * Age [yr] + 120.6; $r = .61, p < .003, n = 30$). As for cortisol nadir concentrations, removing effects of SWS and REM sleep did not significantly alter the correlation between age and mean cortisol concentrations. Unlike cortisol nadir and mean concentrations, nocturnal maximum concentrations of cortisol were not significantly correlated with age ($r = .34$). The maxima of cortisol were reached earlier (with reference to sleep onset) the older the subject was (linear regression equation: Cort max latency [min] = −.32 * Age [yr] + 109.9; $r = -.44, p < .05, n = 20$).

As for the GH maximum values, cortisol nadir concentrations were transformed to percent values with the mean cortisol concentrations of the night set to 100%. These transformed values of cortisol nadir concentrations also increased with age ($r = .89, p < .001, n = 30$; Figure 2).

Representative sleep and hormone profiles of a young (26 yr) and an elderly subject (87 yr) are presented in Figure 3.

Figure 2. Maximum growth hormone (GH) concentrations and cortisol nadir concentrations expressed as percent values with reference to respective nocturnal mean concentrations which were set 100% ($n = 30$). Note that decreases in GH peak concentrations and increases in cortisol nadir concentrations are still present after transformation, indicating that effects of age on GH peak concentrations and cortisol nadir concentrations were more pronounced than those on the respective nocturnal mean concentrations.

Discussion

This study confirmed what has been demonstrated in numerous previous studies, that elderly humans have less SWS, less REM sleep (6,7), diminished nocturnal GH surges (6,8), and a phase advance of the nocturnal maximum of cortisol secretion in comparison to younger controls (6). Together, these results prove the present subject sample to be representative of a normal population.

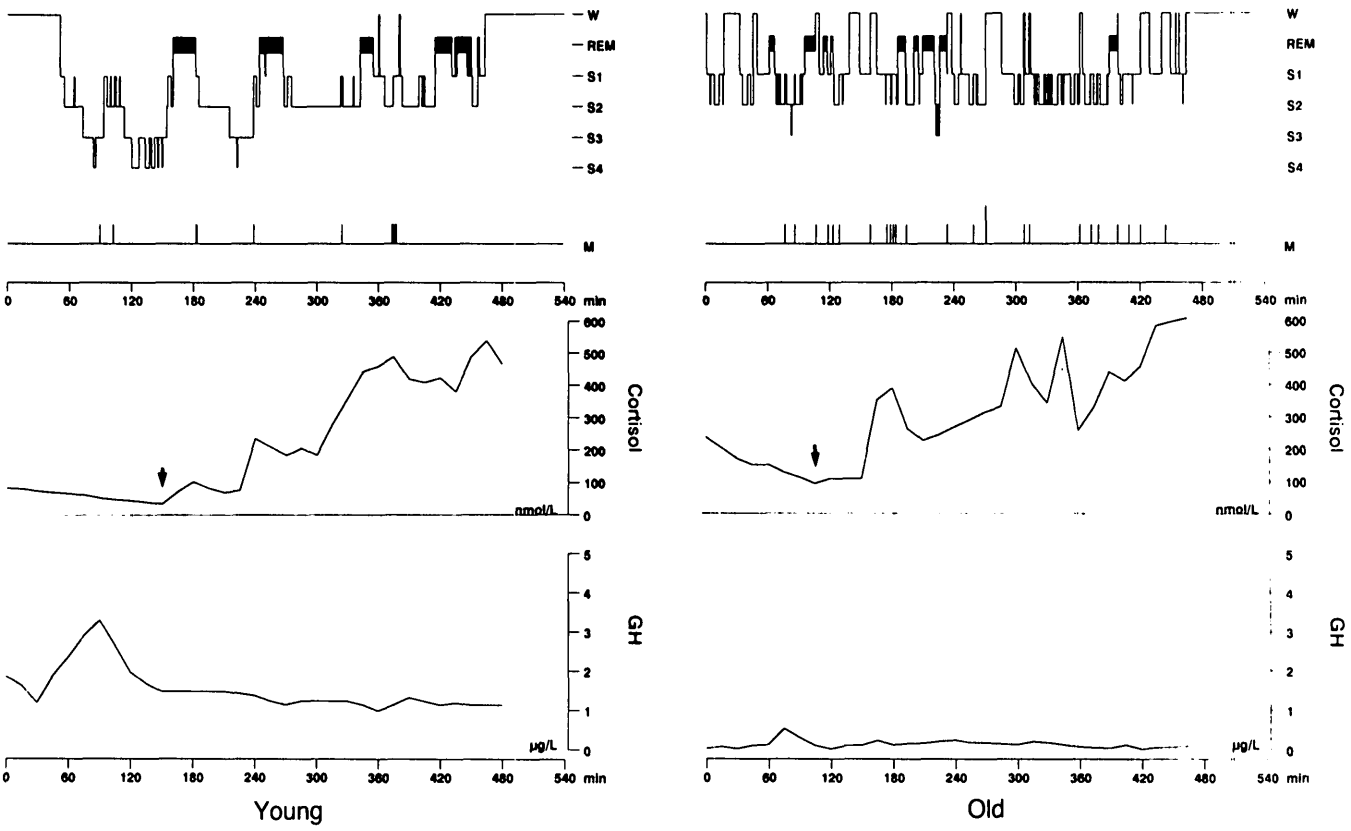

Figure 3. Representative sleep (top), cortisol (middle), and GH profiles (bottom) of a young (26 yr; left panel) and an old subject (87 yr; right panel). Note the decrease in the time spent in SWS and REM sleep as well as the decrease in maximum GH concentration and the increase in cortisol nadir concentration (arrow) in the first half of sleep time in the older subject as compared to the younger subject.

As yet, the time course of changes in sleep-dependent GH secretion across age in humans has not been investigated. The present results indicate that in subjects as young as 30–40 yr, GH peak and mean concentrations during the night fall dramatically, and that they remain at a low level beyond the age of 50 yr. This could be of considerable relevance for the timing of a GH replacement therapy in elderly people (14).

The reduced sleep-associated GH secretory peak, stimulated most probably by hypothalamic release of GH-releasing hormone (GHRH) (17), may be due to a diminished pituitary responsiveness to GHRH in elderly people (18). Also, release of somatostatin, inhibiting the stimulating effect of GHRH (19), may be increased in elderly people.

The reduction of GH secretory peaks was paralleled by a decrease in time spent in SWS with increasing age, suggesting a link between the central nervous generators of SWS and hypothalamo-pituitary regulation of GH secretion. However, in young men, acute selective deprivation of SWS did not alter sleep-related GH secretion (2), and a single administration of GH did not affect the time spent in SWS in young subjects (20). These findings argue against the view that diminished GH secretory activity is a consequence of diminished SWS, and vice versa. Rather, the parallel decreases in GH secretion and SWS with increasing age suggest an effect of age on a common central nervous mechanism with a regulatory influence on both SWS and GH secretory activity. Recent work by Van Cauter and co-workers (21,22) and Steiger and co-workers (23) has provided indirect evidence that such a mechanism could be coupled to the hypothalamic synthesis of GHRH. In those studies, the pulsatile administration of GHRH has been shown to increase both time spent in SWS and GH concentrations during nighttime sleep. This view is further supported by the partial correlation analysis between age and maximum GH concentrations, indicating the influence of age on GH secretion to be linked to age-dependent changes in sleep.

The cortisol nadir occurring within the first two NonREM/REM sleep cycles of undisturbed sleep and also mean cortisol concentrations during the night increased linearly with increasing age. Peak concentrations of nocturnal cortisol did not change with age. Removing effects of SWS and REM sleep by determining partial correlation coefficients indicated that changes in cortisol nadir concentrations with age were independent of those of sleep. This suggests a particular significance of the increase in cortisol nadir concentrations in the process of aging.

This pattern of results adds to previous findings of an age-related linear trend toward increased basal levels of plasma cortisol in animals and in humans (6,8,9,24,25). An age-dependent increase in basal cortisol secretion has been found also in baboons, yet this increase appeared to follow a nonlinear function (26). Others failed to find differences in basal cortisol secretion between young and elderly subjects (27–30). But, in these studies, basal cortisol levels were assessed at different times of the day and while subjects were awake. Hence, circadian rhythms and pituitary adrenal secretory responses to exogenous stress could have contaminated evaluation of basal secretory activity in these studies. Here, basal cortisol levels were assessed during undisturbed sleep, a time when adrenal secretory activity appears to depend almost exclusively on endogenous rhythmicity, and is not contaminated by any exogenous stress.

The finding of increasing basal cortisol, but unchanged peak concentrations of cortisol with age, fits previous results of an age-related decrease in the amplitude of circadian fluctuations found, for instance, for core body temperature (31), melatonin and thyrotropin secretion, and sleep processes (6). This suggests a common circadian pacemaker to be altered in elderly people, which may entrain sleep and hypothalamo-pituitary-adrenal (HPA) secretory activity by synchronized inhibitory or stimulatory influences on the respective sleep and endocrine centers in brainstem and hypothalamus. However, the age-related increase in cortisol nadir concentrations in the present study was found to be independent of the decrease of SWS and REM sleep in elderly people; this indicates that separate mechanisms are responsible for the increased cortisol nadir concentration and reduced SWS and REM sleep in elderly people. Animal studies have provided evidence that enhanced cortisol nadir concentrations result from an impaired negative feedback inhibition of pituitary-adrenal activity (27), which is mediated by hippocampal type I corticosteroid receptors (13), and therefore may interfere with the circadian regulation of HPA secretory activity. The feedback in elderly people could be impaired due to a loss of hippocampal type I corticosteroid receptors (13,32). Confirmatory evidence for this view comes from a recent study, demonstrating that blocking type I corticosteroid receptors by canrenoate in young subjects increased basal cortisol secretion during the first half of nocturnal sleep (11).

The increase in cortisol nadir concentrations in aged subjects coincided with an age-dependent decrease in SWS, as indicated by a moderate but significant negative correlation between these parameters. This relation contrasts with findings in young subjects of an enhanced time spent in SWS during infusion of cortisol at physiological concentrations (33,34). However, inducing similarly elevated cortisol levels by a constant infusion of ACTH did not affect SWS (34), indicating that ACTH, per se, reduces SWS. Evidence exists that in elderly people the increase in nocturnal ACTH levels exceeds that of cortisol (35); this suggests that in aged persons, in fact, decreasing influences of pituitary-adrenal hormones on SWS prevail.

The age-dependent decrease in GH peak concentrations and the increase in cortisol nadir concentrations remained when concentrations were expressed in percent with nocturnal mean concentrations set to 100% (Figure 2). This indicates that effects of age on GH peak concentrations and cortisol nadir concentrations were more pronounced than those on the respective nocturnal mean concentrations. Thus, the age-related decrement in the ability to maximally secrete GH and to maximally suppress cortisol secretion was greater than the overall age-related changes in these hormone systems. So, the most pronounced changes in GH and cortisol secretion occurred during the first two NonREM/REM sleep cycles, at a time when maximum GH levels coincide with nadir concentrations of cortisol. This inverse relation between GH and cortisol concentrations appears to

be a crucial feature of nocturnal sleep. During diurnal wakefulness, GH and cortisol typically rise together in response to external stressors. Recent findings that the GH response to exogenous GHRH is increased by sleep (36), while the cortisol response to exogenous corticotropin-releasing hormone (CRH) is suppressed by sleep (5), further support a functional role of sleep enabling GH secretion uncontaminated by a significant cortisol release. In fact, evidence exists that the magnitude of the anabolic response to GH is attenuated with increased cortisol levels (37,38) even within the physiological range (39). The ratio of GH maximum concentration to cortisol nadir concentration is diminished in elderly people, suggesting that, in addition to a diminished GH release, the anabolic response to GH is further attenuated by increased cortisol nadir concentrations. This view fits well with the clinical observation of a skin and muscle atrophy associated with aging.

In sum, the data indicate that alterations of GH peak amplitude and basal cortisol secretion are not restricted to senescence, but begin in the first third of adult life and then gradually become more evident with increasing age. Changes in both GH and cortisol secretion may act together to reduce anabolic functions of sleep in the aged.

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