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Sleep Loss

Sleep Loss Results in an Elevation of Cortisol Levels the Next Evening

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Summary: Sleep curtailment constitutes an increasingly common condition in industrialized societies and is thought to affect mood and performance rather than physiological functions. There is no evidence for prolonged or delayed effects of sleep loss on the hypothalamo-pituitary-adrenal (HPA) axis. We evaluated the effects of acute partial or total sleep deprivation on the nighttime and daytime profile of cortisol levels. Plasma cortisol profiles were determined during a 32-hour period (from 1800 hours on day 1 until 0200 hours on day 3) in normal young men submitted to three different protocols: normal sleep schedule (2300–0700 hours), partial sleep deprivation (0400–0800 hours), and total sleep deprivation. Alterations in cortisol levels could only be demonstrated in the evening following the night of sleep deprivation. After normal sleep, plasma cortisol levels over the 1800–2300-hour period were similar on days 1 and 2. After partial and total sleep deprivation, plasma cortisol levels over the 1800–2300-hour period were higher on day 2 than on day 1 (37 and 45% increases, $p = 0.03$ and 0.003, respectively), and the onset of the quiescent period of cortisol secretion was delayed by at least 1 hour. We conclude that even partial acute sleep loss delays the recovery of the HPA from early morning circadian stimulation and is thus likely to involve an alteration in negative glucocorticoid feedback regulation. Sleep loss could thus affect the resiliency of the stress response and may accelerate the development of metabolic and cognitive consequences of glucocorticoid excess. **Key Words:** Sleep loss—Hypothalamo-pituitary-adrenal axis—Cortisol—Aging—Stress.

Sleep loss represents an increasingly common condition in industrialized societies (1–4). Our society attaches an economic and moral value to sleeping as little as possible to extend the waking period to the longest tolerable limit. Around-the-clock operations imply chronic partial sleep loss for the large population of shift workers and the repeated occurrence of acute total sleep deprivation for certain key personnel (3). Although the consequences of endemic sleep loss for human performance and safety have recently received public attention (2), possible adverse effects on health have received little, if any, attention.

Studies that have examined physiological markers of stress, such as urinary levels of cortisol and catecholamines or blood levels of cortisol, have failed to obtain evidence suggesting that sleep loss may constitute a stressful condition (5–9). As far as cortisol levels are concerned, this negative finding is consistent with the fact that the normal 24-hour variations of activity of the hypothalamo-pituitary-adrenal (HPA) axis, the major neuroendocrine transducer of stress, are primarily regulated by circadian rhythmicity and are only minimally modulated by sleep (10). Indeed, sleep onset exerts a modest inhibitory effect on cortisol secretion for 1 to 2 hours, nocturnal awakenings are consistently followed by a pulse of cortisol secretion, and, at the end of the sleep period, the final sleep–wake transition further elevates the high morning concentrations of peripheral cortisol levels (11–14). The only known effects of total sleep deprivation on HPA function correspond to the absence of these immediate responses to sleep–wake transitions.

The aim of the present study was to evaluate the effects of acute partial or total deprivation of nocturnal sleep on the profile of plasma cortisol levels on the next day.

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METHODS

A total of 33 healthy, nonobese young men were studied. All subjects were nonsmokers and had no personal endocrine illness or sleep disorders. Positive criteria for selection included regular life habits and sleep schedules. Shift workers and subjects who had having experienced transmeridian flights within the last 6 weeks were excluded from the study. The protocol was approved by the Institutional Review Board of the University of Chicago, and all subjects gave written informed consent.

Before the start of the study, all subjects were habituated to the laboratory environment by spending 2 nights in the Clinical Research Center of the University of Chicago. The subjects were studied during a continuous 32-hour period, starting at 1800 hours on day 1 until 0200 hours on day 3. They were aware of local clock time, and during wakeful periods, they watched television, read, and engaged in conversations with members of the staff. They remained recumbent throughout the study. They were maintained in dim light during waking periods and in complete darkness during the sleep periods. Food intake was replaced by an intravenous glucose infusion at a constant rate of 5 g/kg every 24 hours.

Nine subjects [22–32 years old, body mass index (BMI) 22.8 ± 1.0 kg/m^2 (mean ± SEM)] were submitted to a normal sleep schedule, i.e. from 2300 to 0700 hours. Seven other subjects (22–30 years old, BMI 24.7 ± 0.7 kg/m^2) were submitted to a sleep–wake schedule involving enforced wakefulness until 0400 hours and sleep from 0400 to 0800 hours (partial sleep deprivation). The remaining 17 subjects (20–30 years old, BMI 22.7 ± 0.5 kg/m^2) were submitted to continuous wakefulness during the 32 hours of the study (total sleep deprivation). The cortisol profiles from the subjects in the normal sleep group and in the total sleep deprivation group were baseline data obtained in the course of studies on glucose regulation (12) or phase-shifting effects of light (15). The present experimental design allows for the comparison of evening cortisol levels (over the 1800–2300-hour period) before and after normal sleep, partial sleep deprivation, and total sleep deprivation.

A sterile heparin-lock catheter was inserted in the forearm at 1400 hours, and, starting at 1800 hours, blood samples (1 ml) for plasma cortisol determinations were drawn at 20-minute intervals throughout all studies, except during the period from 0400 to 1600 hours in the partial sleep deprivation protocol, when the sampling interval was 60 minutes. The intravenous (IV) line was kept patent with a slow drip of heparinized saline. During sleep hours, the IV line was connected to plastic tubing that extended to an adjoining room, as previously described (16). Polygraphic sleep recordings were obtained during all sleep periods (17).

Plasma cortisol levels were determined using the Coat-A-Count kit (Diagnostic Products Corporation, Los Angeles, CA), a direct solid-phase radioimmunoassay using radioiodinated cortisol. The lower limit of sensitivity was 13.8 nmol/l (i.e. 0.5 μg/dl). The intra-assay coefficient of variation averaged 5%. All samples from the same subject were analyzed in the same assay.

Significant cortisol secretory pulses were identified and characterized using a computer program (ULTRA) previously described (18). A pulse was considered significant if both its increment and its decline exceeded, in relative terms, twice the intra-assay coefficient of variation.

The onset of the nocturnal quiescent period of cortisol secretion was defined as the time when plasma cortisol level reached a value lower than 138 nmol/l (i.e. 5 μg/dl), provided that such low values were maintained in at least three consecutive samples.

Statistical calculations were performed using the nonparametric Wilcoxon signed-ranks test. All the results are expressed as mean ± standard error of the mean (SEM).

RESULTS

In all individuals, polygraphic sleep recordings were consistent with normal sleep in young adult subjects under laboratory conditions.

Figure 1 (left panels) shows the transverse mean profiles of cortisol levels in the three study conditions. In all three groups, mean cortisol profiles conformed with the normal classical pattern of cortisol secretion (10), with lower concentrations in the late evening and in the first part of the night, followed by an abrupt elevation to reach a morning maximum at 0700–0900 hours and a subsequent progressive decline during the late morning and the afternoon.

The shaded areas (Fig. 1, left panels) illustrate the areas under the curve during the time interval 1800–2300 hours on days 1 and 2, i.e. during a 5-hour period of normal waking (preceding usual bedtime) common to all three experimental groups. Mean cortisol values over the 1800–2300-hour period on both days in the three experimental conditions are shown in the right panels of Fig. 1. In the absence of sleep deprivation (normal sleep group, upper panels of Fig. 1), cortisol levels over the time period 1800–2300 hours were similar on both experimental days, averaging 135 ± 17 nmol/l (4.9 ± 0.6 μg/dl) on day 2 vs. 130 ± 11 nmol/l (4.7 ± 0.4 μg/dl) on day 1. In contrast, both partial sleep loss (middle panels of Fig. 1) and total sleep loss (lower panels of Fig. 1) were followed by

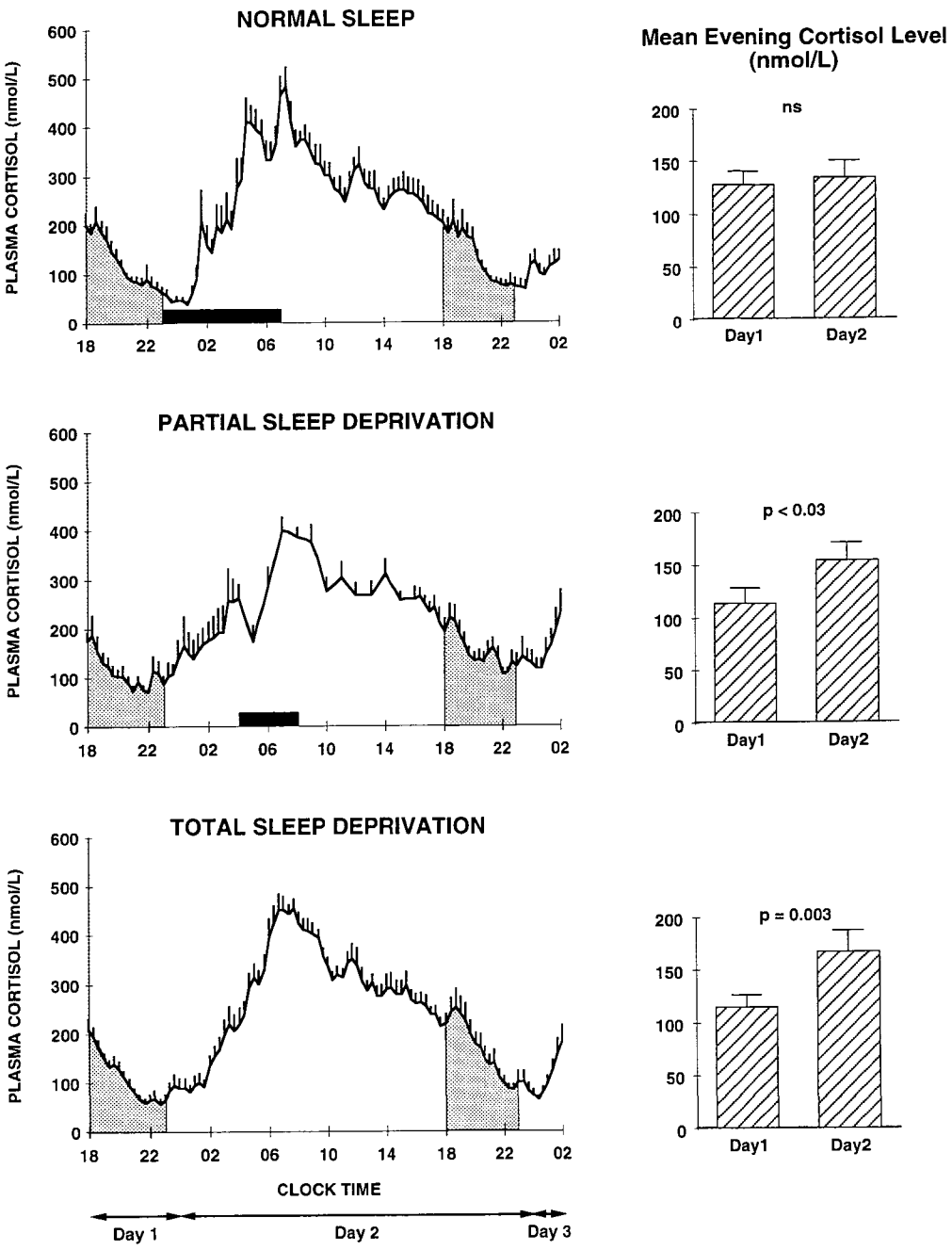

FIG. 1. Left panels: Transverse mean [+ standard error of the mean (SEM)] profiles of cortisol levels in the three experimental conditions. Black bars denote sleep periods. The shaded areas highlight cortisol levels during the time interval 1800–2300 hours on days 1 and 2. Right panels: Mean (+ SEM) cortisol values over the 1800–2300 period on days 1 and 2 in the three experimental conditions. Conversion factor for cortisol concentrations: 1 nmol/l = 27.59 μg/dl.

significant increases in cortisol levels over the 1800–2300-hour period on the second day compared with the first day. After partial sleep deprivation, mean cortisol levels were 155 ± 17 nmol/l (5.6 ± 0.6 μg/dl) vs. 113 ± 14 nmol/l (4.1 ± 0.5 μg/dl) on the preceding day ($p < 0.03$), i.e. a 37% increase. After total sleep deprivation, mean cortisol levels were 168 ± 19 nmol/l (6.1 ± 0.7 μg/dl) vs. 116 ± 11 nmol/l (4.2 ± 0.4 μg/dl) on the preceding day ($p = 0.003$), i.e. a 45% increase.

Individual cortisol profiles of representative subjects in each experimental condition are shown in Fig. 2 (left panels). For each group, the mean increments of pulses detected during the 1800–2300-hour period on both days are shown in the right panels of Fig. 2. Although pulse increments were similar on days 1 and 2

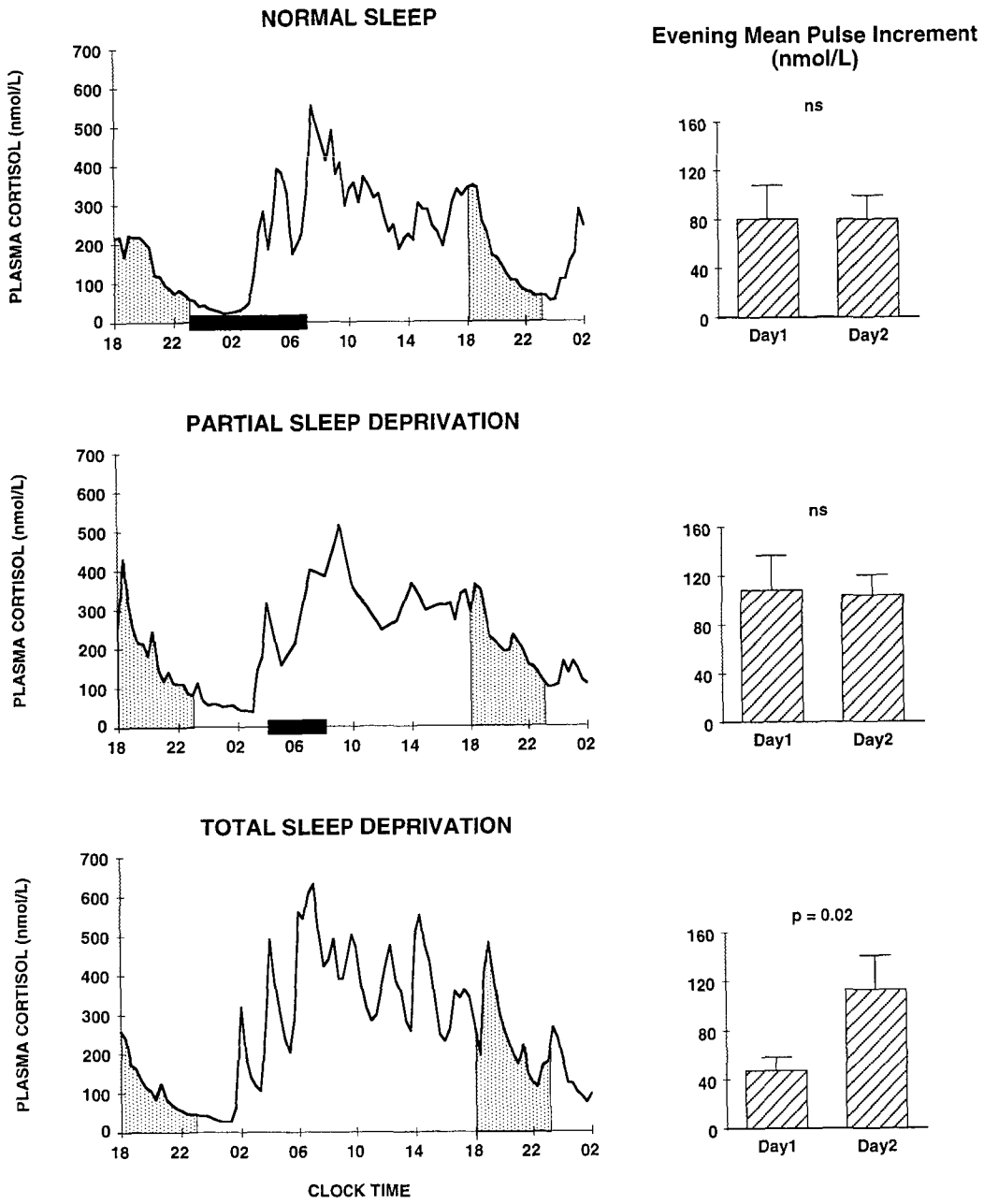

FIG. 2. Left panels: Individual cortisol profiles of representative subjects in each experimental condition. Black bars denote sleep periods. The shaded areas highlight cortisol levels during the time interval 1800–2300 hours on days 1 and 2. Right panels: Mean (+ SEM) pulse increments over the 1800–2300 period on days 1 and 2 in the three experimental conditions. Conversion factor for cortisol concentrations: 1 nmol/l = 27.59 μg/dl.

TABLE 1. *Onset of the quiescent period (clock time in hours ± minutes)*

	Day 1	Day 2	p level
Normal sleep	1938 ± 21	1942 ± 23	NS
Partial sleep deprivation	1909 ± 28	2043 ± 44	0.04
Total sleep deprivation	1938 ± 21	2040 ± 22	0.02

NS, not significant.
Values express mean ± standard error of the mean.

after normal sleep and after partial sleep deprivation, total sleep deprivation was followed by a 2.4-fold increase compared with the baseline ($p = 0.03$). No modification of pulse frequency was detected in any group.

Data concerning the onset of the quiescent period in all experimental conditions are summarized in Table 1. In the absence of sleep deprivation, this measure of the rate of recovery from the early morning elevation was similar on days 1 and 2. After partial and after

total sleep deprivation, the onset of the quiescent period was delayed, on average, by at least 1 hour on day 2 compared with day 1 ($p = 0.04$ at least).

DISCUSSION

It is generally thought that on the day following a night of total or partial sleep deprivation, vigilance, mood, and cognitive function are altered, but physiological variables are not affected. The present data show that the effects of sleep deprivation also include alterations in HPA function. Indeed, sleep deprivation in normal young men, whether total or partial, was followed 12–24 hours later by a delay in the return to quiescence of cortisol secretion, resulting in an elevation of evening cortisol levels, mainly due to an increase in the amplitude of secretory pulses. Thus, the normal daylong decline in cortisol concentrations that follows the early morning circadian elevation appears to occur at a slower rate. These findings suggest that the mechanism of HPA recovery from stimulation, i.e. the glucocorticoid negative feedback mediated by hippocampal function (19,20), may be affected by sleep loss. Thus, sleep loss does not appear to constitute an acute stimulus for the HPA axis, i.e. a "stressor", but instead affects the rate of recovery, i.e. the resiliency, of the HPA response to endogenous stimulation by circadian rhythmicity. Our findings also raise the possibility that the resiliency of the HPA axis to exogenous stimulation by stressors may also be affected by sleep loss.

Both animal and human studies have indicated that deleterious central as well as metabolic effects of HPA hyperactivity are much more pronounced at the time of the usual trough of the rhythm (i.e. in the evening in the human) than at the time of the peak (i.e. in the morning in the human) because, at the trough of the rhythm, both the high-affinity type I (mineralocorticoid) receptors in the hippocampus and the low-affinity type II (glucocorticoid) receptors in the central nervous system and in the periphery are largely unoccupied (21). Thus, the modest elevations in evening cortisol levels that were observed in individuals exposed to acute sleep deprivation could, under conditions of chronic sleep loss, facilitate the development of central as well as peripheral disturbances associated with glucocorticoid excess, such as memory deficits due to impaired hippocampal function (19) and insulin resistance (21).

The same alteration in HPA regulation after sleep loss is found in this study as is found in normal aging (22), which is also associated with increased evening levels of plasma cortisol and decreased resiliency of the HPA axis (23,24). Rodent studies have indicated that aging is associated with a feed-forward cascade of negative effects, where increased exposure to glucocorticoids impairs the resiliency of the HPA axis, resulting in further increases in glucocorticoid exposure and further impairment of the ability to recover from stimulation (25). Thus, cumulative stress exposure may accelerate senescence through increased cumulative exposure to glucocorticoids (26). The present data further suggest that age-related sleep disorders could be involved in this feed-forward cascade of negative effects. Indeed, the fragmentation of sleep that typically occurs in the elderly (27) is likely to result in elevated evening cortisol secretion and, because nocturnal exposure to increased HPA activity may promote sleep fragmentation (28,29), is also likely to further impair sleep quality.

Although a matter of debate (30), most recent studies indicate that populations of developed countries are chronically sleep deprived because of their socioeconomic and cultural environments (1–3). A recent report has indicated that the incidence of symptoms associated with insufficient sleep has increased over the past 50 years (4). Chronic sleep deprivation affects at least one-third of normal American adults (31). The present data suggest that in addition to the effects on mood and alertness and the adverse consequences for performance and safety, chronic voluntary sleep curtailment, which is increasingly prevalent, may have long-term adverse health effects.

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