

Chronic Insomnia Is Associated with Nyctohemeral Activation of the Hypothalamic-Pituitary-Adrenal Axis: Clinical Implications

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Although insomnia is, by far, the most commonly encountered sleep disorder in medical practice, our knowledge in regard to its neurobiology and medical significance is limited. Activation of the hypothalamic-pituitary-adrenal axis leads to arousal and sleeplessness in animals and humans; however, there is a paucity of data regarding the activity of the hypothalamic-pituitary-adrenal axis in insomniacs. We hypothesized that chronic insomnia is associated with increased plasma levels of ACTH and cortisol. Eleven young insomniacs (6 men and 5 women) and 13 healthy controls (9 men and 4 women) without sleep disturbances, matched for age and body mass index, were monitored in the sleep laboratory for 4 consecutive nights, whereas serial 24-h plasma measures of ACTH and cortisol were obtained during the fourth day. Insomniacs, compared with controls, slept poorly (significantly higher sleep latency and wake during baseline nights). The 24-h ACTH and cortisol secretions were significantly higher in insomniacs, compared with normal controls (4.2 ± 0.3 vs. 3.3 ± 0.3 pm, $P = 0.04$; and 218.0 ± 11.0 vs. 190.4 ± 8.3 nm, $P = 0.07$). Within the 24-h period, the greatest elevations were observed in the evening and first half of the night. Also, insomniacs with

a high degree of objective sleep disturbance (% sleep time < 70), compared with those with a low degree of sleep disturbance, secreted a higher amount of cortisol. Pulsatile analysis revealed a significantly higher number of peaks per 24 h in insomniacs than in controls ($P < 0.05$), whereas cosinor analysis showed no differences in the temporal pattern of ACTH or cortisol secretion between insomniacs and controls. We conclude that insomnia is associated with an overall increase of ACTH and cortisol secretion, which, however, retains a normal circadian pattern. These findings are consistent with a disorder of central nervous system hyperarousal rather than one of sleep loss, which is usually associated with no change or decrease in cortisol secretion or a circadian disturbance. Chronic activation of the hypothalamic-pituitary-adrenal axis in insomnia suggests that insomniacs are at risk not only for mental disorders, i.e. chronic anxiety and depression, but also for significant medical morbidity associated with such activation. The therapeutic goal in insomnia should be to decrease the overall level of physiologic and emotional arousal, and not just to improve the nighttime sleep. (*J Clin Endocrinol Metab* 86: 3787–3794, 2001)

INSOMNIA is, by far, the most commonly encountered sleep disorder in medical practice (1, 2). Either as a symptom of various psychiatric or medical disorders or as the result of a stressful situation, chronic and severe insomnia is perceived by the patient as a distinct disorder (3). Both patients and practicing physicians find the treatment of chronic insomnia challenging, often unsatisfactory, and frequently frustrating. The long list of recommended therapeutic approaches, and the fact that none of them is truly effective, is clear evidence of the therapeutic difficulties associated with this disorder and reflects our limited understanding of its neurobiology. This limited understanding may be at the basis of chronic unresolved questions about the nosology, etiol-

ogy, and treatment of chronic insomnia (4). An additional compounding factor is that physicians, including even sleep researchers, tend to view insomnia and the associated complaints of poor mental and physical health as obsessions of otherwise healthy individuals (5).

Since the early 1970s, many studies have demonstrated a strong association between insomnia and psychologic factors, especially in relation to perceived stress (1–4). Stress has been associated with activation of the hypothalamic-pituitary-adrenal (HPA) axis (6), while CRH and cortisol, respectively the hypothalamic and adrenal products of the HPA axis, both lead to arousal and sleeplessness in humans (7, 8) and animals (9, 10). Conversely, sleep, particularly deep sleep, has an inhibitory influence on the stress system, of which the HPA axis is a major component (11, 12). Despite this evidence linking sleep and the HPA axis, there is a paucity of studies assessing HPA axis activity in insomnia. One early study failed to show any differences in urinary cortisol excretion between controls and poor sleepers (13). Recently, in a preliminary study, we demonstrated that in

Abbreviations: AUC, Area under the curve; BMI, body mass index; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition; HPA, hypothalamic-pituitary-adrenal; MANOVA, multivariate ANOVA; MESOR, midline estimating statistic of rhythm; MMPI, Multiple Minnesota Personality Inventory; REM, rapid eye movement; SL, sleep latency; ST, sleep time; TWT, total wake time; WTASO, wake time after sleep onset.

young adult insomniacs, 24-h urinary free cortisol excretion was positively correlated with polysomnographic indices of sleep disturbance (14).

The goal of this study was to examine the 24-h quantitative, pulsatile, and temporal pattern of ACTH and cortisol secretion and the sleep parameters in insomniacs and controls matched for age and body mass index (BMI). We hypothesized that insomnia would be associated with increased plasma levels of ACTH and cortisol and that there would be a positive correlation between the severity of insomnia and the degree of HPA axis activation.

Subjects and Methods

Eleven (6 men and 5 women) young insomniacs and 13 (9 men and 4 women) age- and BMI-matched healthy controls (mean \pm SD age, 31.4 ± 6.7 vs. 27.7 ± 6.8 yr, not significant; mean \pm SD BMI, 25.0 ± 3.7 vs. 25.5 ± 3.9 , not significant) participated in the study. The subjects were recruited from the community, through a newspaper advertisement, and from the medical and technical staff and students of the Milton S. Hershey Medical Center.

A complete medical history was recorded, and a complete physical examination was performed, including mental status assessment and a battery of clinical tests (including complete cell blood count, urinalysis, thyroid indices, and electrocardiogram). All potential research subjects were interviewed and then required to complete a comprehensive questionnaire and a Multiple Minnesota Personality Inventory (MMPI)-II. The questionnaire provided a detailed history of sleep habits, sleep complaints, general health, medication use, tobacco use, and consumption of caffeinated beverages.

Eligibility criteria for insomniacs included a history of difficulty falling asleep (taking 45 or more min to fall asleep) and/or staying asleep [obtaining fewer than 6.5 h of total sleep time (ST)] at least 4 nights a week for at least 6 months. In addition, insomniacs had to demonstrate a sleep efficiency of less than 80% during a screening night in the sleep laboratory. Insomniacs were evaluated by a psychiatrist (Alexandros N. Vgontzas, M.D.), and those who met the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) criteria of a current mental disorder (*i.e.* major depression, psychosis, generalized anxiety disorder, panic disorder, or substance abuse) were excluded from the study.

Both insomniacs and controls were in good physical health, not using any medication for at least a month, and not doing shift work, and the battery of clinical tests were negative for abnormal findings. All subjects were screened in the sleep laboratory for sleep disordered breathing, nocturnal myoclonus, or other primary sleep disorders. Finally, controls had no sleep complaints, whereas during the screening night they had to demonstrate a sleep efficiency of more than 85%. The study was approved by the Institutional Review Board, and each subject signed a written informed consent.

Sleep laboratory recordings

Subjects were recorded in the sleep laboratory for 4 consecutive nights. The first night allowed for adaptation to the new sleeping environment and was not included in the analysis. Sleep laboratory recording was carried out in a sound-attenuated, light- and temperature-controlled room that has a comfortable bedroom-like atmosphere. During this evaluation, each subject was monitored continuously for 8 h. The sleep schedule in the sleep laboratory was similar to the subjects' normal sleep schedule, which was between 2200–2300 to 0600–0700 h. Electroencephalographic, electrooculographic, and electromyographic recordings were obtained in accordance with standard methods (15). The sleep recordings were amplified using standard clinical polygraphs (Grass Instrument Co., Model 78d and e, Quincy, MA). The sleep records were scored independent of any knowledge of the experimental condition, according to standardized criteria (15).

Sleep parameters, assessed from the sleep recordings, included sleep induction (sleep latency, or SL); sleep maintenance (wake time after sleep onset, or WTASO); total wake time (TWT), which is the sum of SL and WTASO; total ST and percent ST (which is total ST, as percent of time

in bed); percentage of the various sleep stages [rapid eye movement (REM), 1, 2, combined 3 and 4 for slow wave sleep, which is calculated as the minutes in each stage as the percent of total ST]; and REM latency, which is the interval from sleep onset to the first REM period. Sleep onset was defined as the latency from lights out to the first occurrence of any stage sleep for a duration of 1 min or longer. If, however, the initial stage of sleep was stage 1, then it had to be followed without any interfering wake, by at least 1 min, of any other stage.

Throughout the study, subjects completed a postsleep questionnaire upon awakening in the morning and estimated time to fall asleep, number of nightly awakenings, total ST, early final awakening, soundness and quality of sleep, and morning sleepiness. Each morning and evening, tension and anxiety were also assessed on a 10-cm analog scale that ranged from extremely calm to extremely agitated conditions. Throughout the study, subjects were instructed not to nap, not to alter their level of physical activity, and not to use any medication.

Blood drawing technique

Twenty-four-hour blood sampling was performed serially, every 30 min, on the fourth day. An indwelling catheter was inserted in the antecubital vein about 30 min before the first blood draw. The catheter was kept patent with small amounts of heparin. During the sleep recording period, blood was collected outside the subjects' room, through a perforation in the wall, via extended tubing, to decrease sleep disturbance from the blood drawing. During the daytime, the subjects were ambulatory; and they were allowed to watch TV, play computer and table games, go to the bathroom, and engage in other similar activities. Also, they were instructed not to change their diet, and their three daily meals were at about 0700, 1200, and 1800 h.

Hormone assays

Blood collected from the indwelling catheter was transferred to an EDTA-containing tube and refrigerated until centrifugation (within 3 h). The supernatant was frozen at -20°C , for the hormones, until assay. ACTH and cortisol levels were measured by specific immunoassay techniques as previously described (16). The lower limit of detection was 5 pg/ml for ACTH and 0.7 $\mu\text{g}/\text{dl}$ for cortisol. The intra- and interassay coefficients were, respectively, 4.6% and 6.0% for cortisol, and 10.0% and 12.0% for ACTH.

Statistical analyses

Baseline sleep and MMPI-II profiles were compared between insomniacs and controls, using *t* tests. Twenty-four-hour serial plasma ACTH and cortisol levels were analyzed using multivariate ANOVA (MANOVA), assuming the covariance type was of a heterogeneous first-order autoregressive structure. In addition, the circadian rhythmicity of ACTH and cortisol secretion was assessed with cosinor-multiple-components rhythmometry (17), by fitting a curve to each individual profile and the entire population profile. This method allowed fitting a model with several cosine functions to the data. The data were analyzed after they were transformed to percent of the mean, which is the preferred approach, to show predictable variability when data are obtained from different individuals (18). Furthermore, the plasma ACTH and cortisol concentrations obtained were analyzed for the presence of pulses, by the Detect program (19). Samples were analyzed for 24-h peak area, peak amplitude, and number of peaks per unit of time.

The association between degree of sleep disturbance and 24-h ACTH and cortisol secretion in controls and insomniacs was assessed by dividing each group into two subgroups, based on median split of the percentage of ST (high total ST vs. low total ST), and comparing their hormonal values using MANOVA. Variability estimates were expressed as SE, with the exception of age and BMI (for which variability was expressed as SD).

Results

Sleep and MMPI-II profiles of insomniacs and controls

Insomniacs, compared with controls during the baseline nights 2 and 3, slept poorly (Table 1). Specifically, insomniacs

demonstrated a longer SL, more WTASO and TWT, and less percentage of ST (all $P < 0.01$). Insomniacs and controls were not different in terms of sleep stage variables. Subjectively, insomniacs (compared with controls) reported longer SL, less amount of sleep, and lighter sleep (all $P < 0.05$). Also, the

TABLE 1. Baseline sleep patterns of insomniac and control subjects

	Insomnia subjects	Control subjects
Sleep efficiency		
SL (min)	32.8 ± 5.2^a	11.0 ± 1.9
WTASO (min)	50.9 ± 11.7^a	22.5 ± 2.6
TWT (min)	83.7 ± 13.4^a	33.5 ± 2.9
% ST	82.5 ± 2.8^a	93.0 ± 0.6
Sleep stages		
% Stage 1	2.8 ± 0.3	3.2 ± 0.5
% Stage 2	66.9 ± 2.0	63.5 ± 2.2
% Slow-wave sleep	8.7 ± 1.7	9.8 ± 1.7
% REM	21.5 ± 1.2	23.5 ± 1.6
REM distribution		
REM latency (min)	84.4 ± 8.8	87.7 ± 5.0
REM interval (min)	101.6 ± 6.6	95.4 ± 2.9
REM duration	22.2 ± 1.6	23.7 ± 1.4
No. REM periods	3.9 ± 0.2^b	4.5 ± 0.2

The data represent average values \pm SE from nights 2 and 3. P values were derived using t test.

^a $P < 0.01$.

^b $P < 0.05$.

group of insomniacs, compared with controls, scored significantly higher in 6/8 MMPI-II clinical scales (hypochondriasis, depression, conversion hysteria, psychopathic deviate, paranoia and psychasthenia). The two highest scores were observed on the depression and psychasthenia scales. Insomniacs, during the days in the sleep laboratory, scored higher (compared with controls) in self-assessed anxiety (2.7 vs. 1.6 in the morning and 3.1 vs. 1.5 in the evening, both $P < 0.05$).

Twenty-four-hour secretion of ACTH and cortisol

The 24-h mean ACTH and cortisol secretions were significantly higher in insomniacs than controls (4.2 ± 0.3 vs. 3.3 ± 0.3 pM, $P = 0.04$; and 218.0 ± 11.0 vs. 190.4 ± 8.3 nM, $P = 0.07$, respectively) (Figs. 1 and 2, and Tables 2 and 3). Within the 24-h period, the stronger elevations were observed in the afternoon (1400–1730 h) and in the late evening and early part of the night (2100–0300 h).

Circadian analysis

Cosinor analyses, both for individual and population data, indicated a significant circadian rhythm, with a multiple component curve including periods with 12 and 24 h both for insomniacs and controls ($P < 0.01$) (Fig. 3). There were no

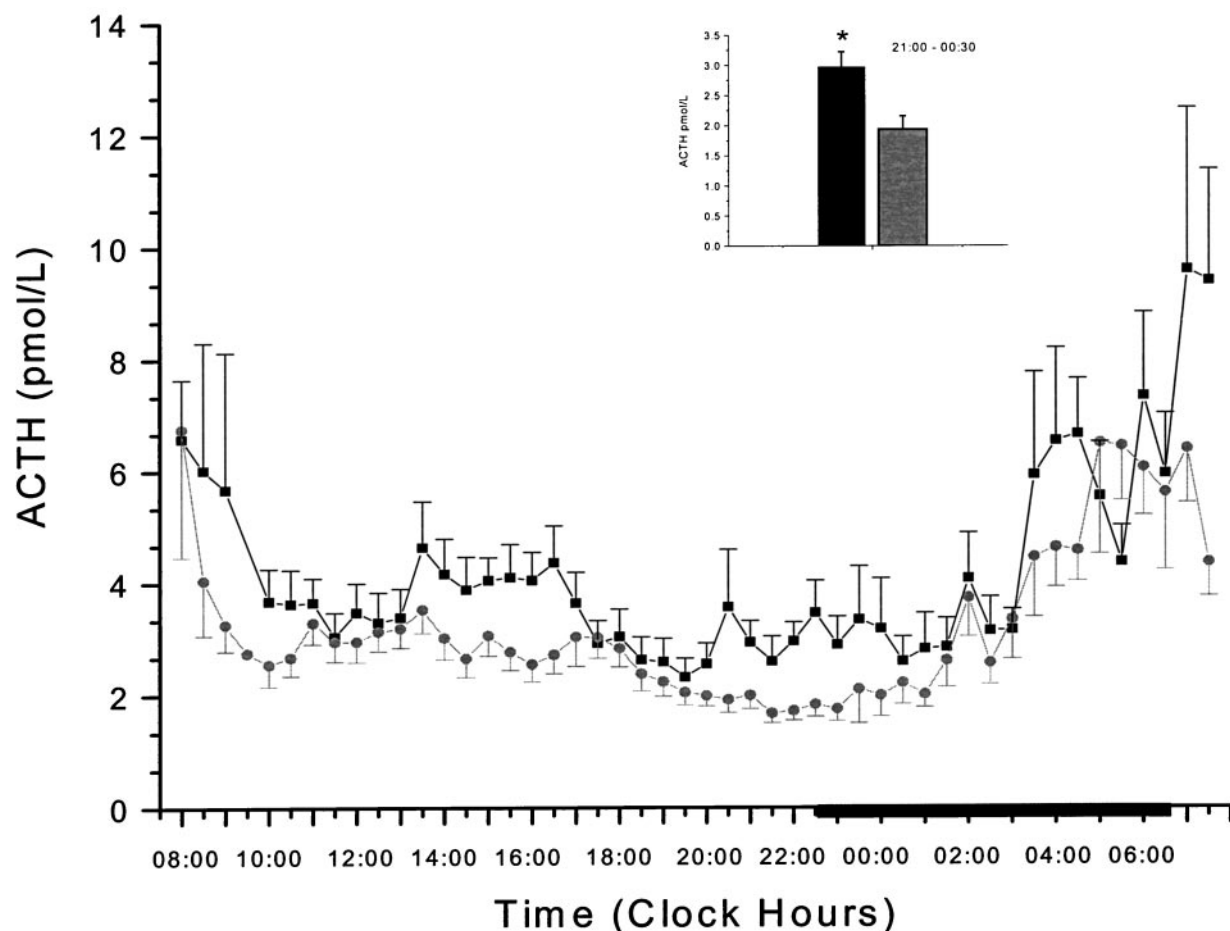


FIG. 1. Twenty-four-hour plasma ACTH concentrations in insomniacs (■) and controls (○). The thick black line indicates the sleep recording period. The error bar indicates SE. *, $P < 0.01$.

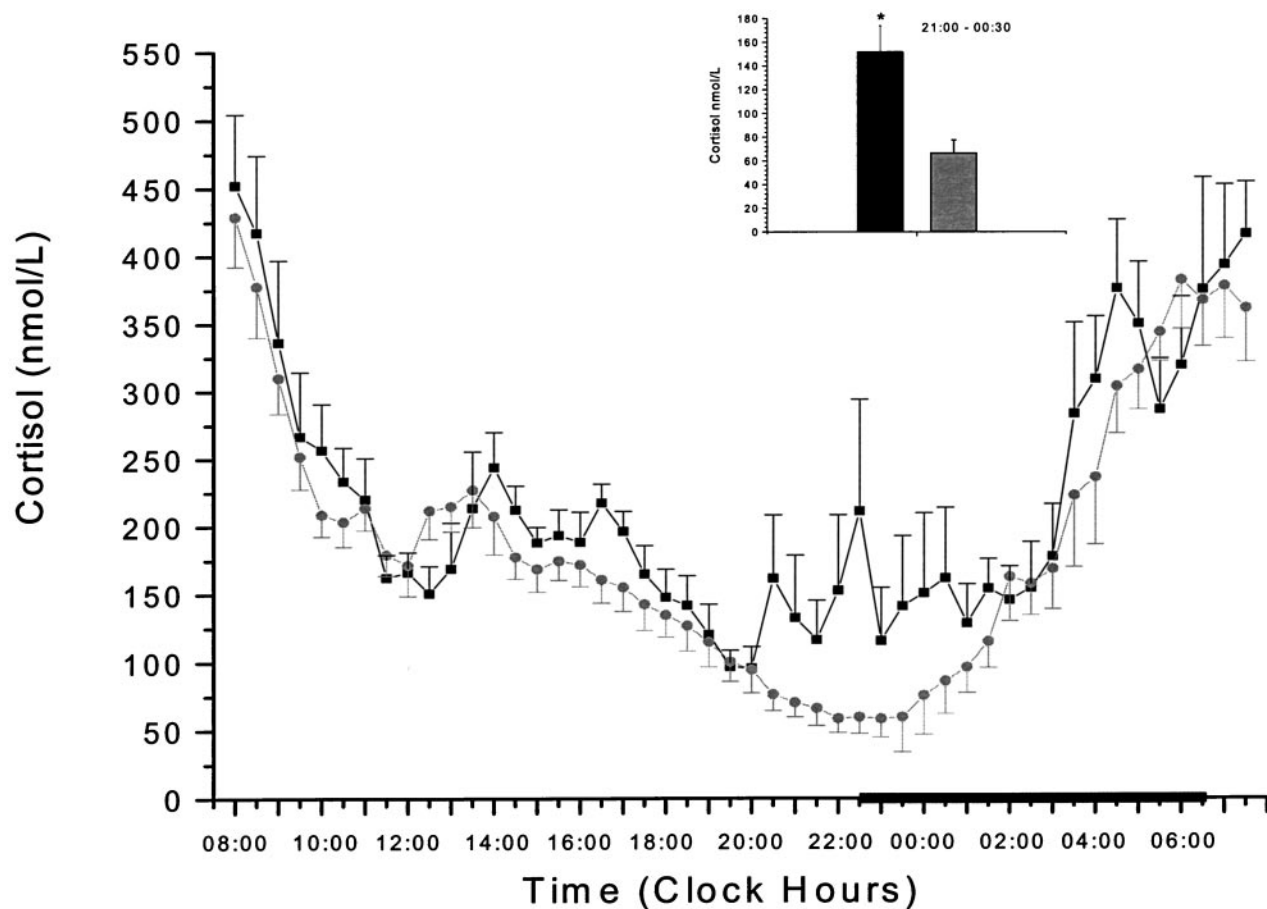


FIG. 2. Twenty-four-hour plasma cortisol concentrations in insomniacs (■) and controls (○). The thick black line indicates the sleep recording period. The error bar indicates SE. *, $P < 0.01$.

TABLE 2. Overall release of ACTH in insomniacs and controls

	Insomniacs	Controls	P-value
Mean values ^a			
24-h (pM)	4.2 ± 0.3	3.3 ± 0.3	0.04
Daytime (0730–2230 h)	4.2 ± 0.4	3.0 ± 0.3	0.01
Morning (0800–1030 h)	5.5 ± 1.2	3.6 ± 1.1	0.23
Lunch (1100–1330 h)	3.6 ± 0.3	3.2 ± 0.3	0.29
Afternoon (1400–1730 h)	3.9 ± 0.3	2.9 ± 0.3	0.01
Dinner (1800–2030 h)	2.8 ± 0.2	2.2 ± 0.2	0.11
Evening/early			
Sleep (2100–0030 h)	3.0 ± 0.3	1.9 ± 0.2	0.004
Sleep (2300–0630 h)	4.4 ± 0.6	3.9 ± 0.5	0.49
Pulsatile analysis			
24-h Peak AUC (pM/min)	131.7 ± 14.4	105.4 ± 11.5	0.16
Average AUC/peak	17.9 ± 1.7	19.0 ± 1.9	0.6
No. peaks	7.4 ± 0.5	5.7 ± 0.5	0.02

P values were derived using MANOVA.

^a Values represent least-square means ± SE from the MANOVA.

differences in the temporal pattern of ACTH or cortisol secretion between the two groups. For both groups, the major peak occurred in the early morning (0530–0700 h), whereas a minor peak occurred in the afternoon (1700 h). The nadirs for ACTH and cortisol were close to sleep onset or the first hour of sleep in both groups. ACTH value variations from the midline estimating statistic of rhythm (MESOR), or rhythm-adjusted mean, were significantly lower between 2200–0000 h. Cortisol value variations from the MESOR were signifi-

cantly higher in insomniacs between 1200–1400 h and lower between 2200–0200 h. The amplitude of the circadian rhythm of cortisol was significantly decreased in insomniacs, compared with controls.

Pulsatile analysis

Pulsatile analysis showed that insomniacs had a higher number of ACTH and cortisol pulses than did controls (Tables 2 and 3). There was no difference in the mean 24-h peak area under the curve (AUC) for ACTH or cortisol between these two groups. Furthermore, there was no difference of AUC/peak of ACTH between insomniacs and controls, whereas the mean AUC/peak of cortisol was significantly lower in the former than the latter.

Sleep disturbance and ACTH and cortisol secretion

Within the insomniacs, those with a high degree of sleep disturbance (% ST < 70), compared with those with a low degree of sleep disturbance, secreted a higher amount of cortisol, particularly in the evening and the nighttime periods (2000–0800 h) (difference, 129.7 ± 41.4 nm, $P < 0.01$) (Fig. 4). There were no significant differences between the two subgroups in terms of ACTH secretion for the entire 24-h period and daytime and nighttime periods. Also, no differences in terms of ACTH or cortisol were observed between

TABLE 3. Overall release of cortisol in insomniacs and controls

	Insomniacs	Controls	P-value
Mean values ^a			
24-h (nM)	218.0 ± 11.0	190.4 ± 8.3	0.07
Daytime (0730–2230 h)	209.7 ± 11.0	187.6 ± 11.0	
Morning (0800–1030 h)	328.3 ± 27.6	298.0 ± 24.8	0.41
Lunch (1100–1330 h)	179.3 ± 19.3	201.4 ± 16.6	0.39
Afternoon (1400–1730 h)	198.6 ± 13.8	168.3 ± 13.8	0.12
Dinner (1800–2030 h)	126.9 ± 13.8	107.6 ± 13.8	0.28
Evening/early			
Sleep (2100–0030 h)	151.7 ± 22.1	66.2 ± 11.0	0.003
Sleep (2300–0630 h)	226.2 ± 22.1	198.6 ± 19.3	0.49
Pulsatile analysis			
24-h Peak AUC (nM/min)	7565.2 ± 849.8	7018.9 ± 342.1	0.53
Average AUC/peak	1084.3 ± 113.1	1476.1 ± 99.3	0.02
No. peaks	7.0 ± 0.3	5.0 ± 0.4	<0.001

P values were derived using MANOVA.

^a Values represent least-square means ± SE from the MANOVA.

controls with high *vs.* low sleep efficiency. Finally, there was no association between MMPI scores and ACTH or cortisol secretion.

Discussion

This is the first controlled study to clearly demonstrate, through objective sleep testing and frequent blood sampling, that chronic persistent insomnia is associated with an overall hypersecretion of ACTH and cortisol. This hypersecretion, although more pronounced in the afternoon and evening/early night, is present throughout the 24-h sleep/wake cycle. These results are consistent with (and extend) our previous preliminary findings, based on 24-h urinary free cortisol measures, that chronic insomnia is associated with an activation of the HPA axis (14).

The pulsatile pattern of ACTH and cortisol secretion indicated a higher number of pulses in insomniacs than controls, whereas the average time-integrated 24-h pulse secretion of either hormone showed no difference between the two groups. These results also indicate that the higher mean 24-h values of ACTH and cortisol secretion in insomniacs are primarily caused by increased levels of these hormones during the valleys of the 24-h pulsatile profile. The pattern of ACTH and cortisol secretion in insomniacs suggests that the hyperactivation of the HPA axis in these patients is different from that described in chronically stressed individuals (20). In the latter group, the evening cortisol elevations were accompanied by a presumed compensatory suppression of their morning cortisol secretion; whereas, in our insomniacs, there was an around-the-clock activation of the HPA axis. These findings suggest that insomniacs have sustained arousal and activation of their stress system and that the pathophysiology of insomnia is probably different from increased perceived stress observed in 20–25% of the adult male population (20).

None of our subjects had a diagnosis of major depression, the presence of which may be associated with HPA axis activation (6). Major depression is a relatively infrequent diagnosis among patients referred to a sleep disorders clinic with a primary complaint of chronic insomnia (1, 4, 21). Also, the MMPI scores in the group of insomniacs are typical for this disorder and are consistent with previous findings that

the personality of insomniacs is characterized by internalizing patterns of anxiety, low-grade depression, and rumination (1, 22). Notably, in our study, there was no association between MMPI scores and ACTH or cortisol secretion.

Chronic insomniacs are characterized by long sleep latencies or increased wake time during the night (1, 23); increased perceived stress, anxiety, or depression (1, 4, 22, 24); increased physiologic activation, as indicated by increased body temperature (13, 25); whole-body metabolic rate (26) or heart rate (25); and increased fatigue and inability to function normally during the day although, in objective sleep testing, they are unable to fall asleep (26, 27). Whether these characteristics are secondary to sleep loss or secondary to complaints of another disorder, *i.e.* a central nervous system hyperarousal state, is still under debate. Our hormonal data support the view that insomnia is a disorder of hyperarousal, which is present throughout the 24-h sleep/wake cycle. Supporting this view is the fact that acute or chronic partial sleep deprivation in healthy controls is associated with behavioral phenomena opposite to that of insomnia, *i.e.* fatigue, objectively confirmed sleepiness, decreased anxiety, and other factors (28). Also, most studies on the effect of sleep loss on cortisol secretion, with the exception of one study that showed a significant increase of cortisol in the evening (29), have reported either no change (30–32) or a decrease in the secretion of cortisol (12). The latter study showed that a night of total sleep loss results in a significant reduction of cortisol secretion the next day (12). These findings, combined with the results of this study, suggest that the pathophysiology of chronic insomnia is most likely different from that of sleep loss. However, the fact that the greatest elevation of cortisol was observed in the evening/first half of the night, as well as that a high degree of sleep disturbance was associated with a higher secretion cortisol, suggests that sleep loss may contribute to the evening elevation seen in insomniacs.

Based on the fact that sleep is regulated by a circadian pacemaker, it is plausible that insomnia is caused by disturbances of the coupling of sleep to this pacemaker (33). Based on this assumption, therapeutic methods, such as melatonin or bright light, have been recommended in chronic insomnia. The temporal analysis of our data does not support the view that circadian disturbances are primary in the etiology of

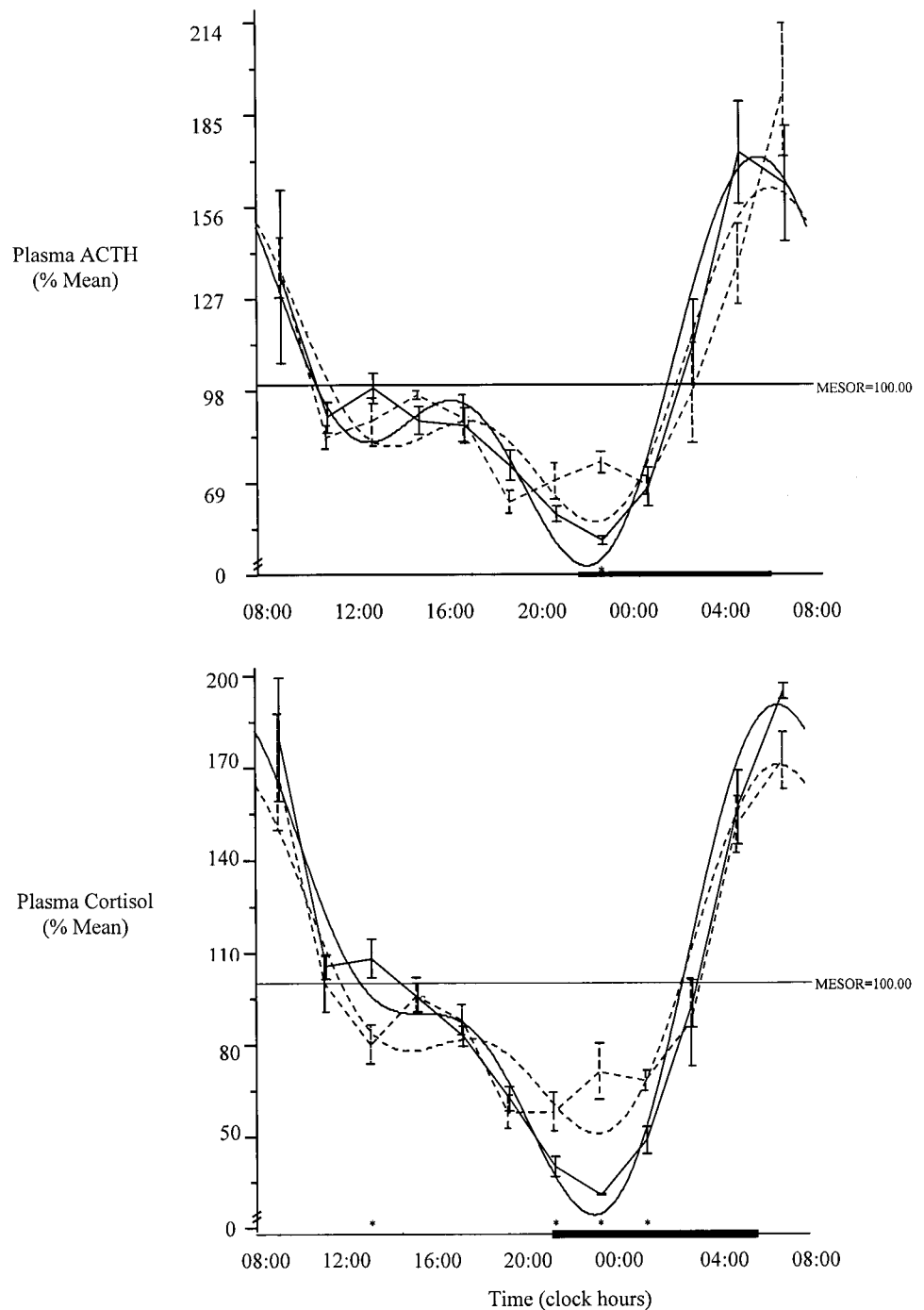


FIG. 3. Multiple component (24 and 12 h) cosinor analysis of 24-h serum ACTH (*top panel*) and cortisol (*bottom panel*) for insomniacs (*dashed line*) and controls (*solid line*), expressed as percent variation from the mean. The *thick black line* on the abscissa represents the sleep recording period. *, $P < 0.05$.

chronic insomnia, at least in the young patients that we studied.

Insomnia is frequently a result of psychologic and psychiatric disturbances (1–4). However, many times, it tends to persist despite the elimination or improvement of the acute perceived stress, anxiety, or depression. Several studies have shown that insomnia precedes, and is a risk factor for, the development of psychiatric conditions, including depression, anxiety, and suicide (2). Our data suggest that it might be possible that activation of the HPA axis in chronic persistent insomnia leads to depression. Indeed, conditions as-

sociated with chronic hypercortisolism, such as Cushing syndrome, of any etiology or chronic unrelieved stress, lead to depression and other psychiatric disturbances (6, 7).

Although the role of insomnia as a risk factor for psychiatric disorders is rather well established, the possibility that chronic insomnia can be associated with significant medical morbidity has not been explored. This is contrary to the extensive research on the effects of another common sleep disorder, *i.e.* sleep apnea, on the cardiovascular system (34). Indeed, no study has assessed systematically the effects of chronic insomnia on the cardiovascular system, including

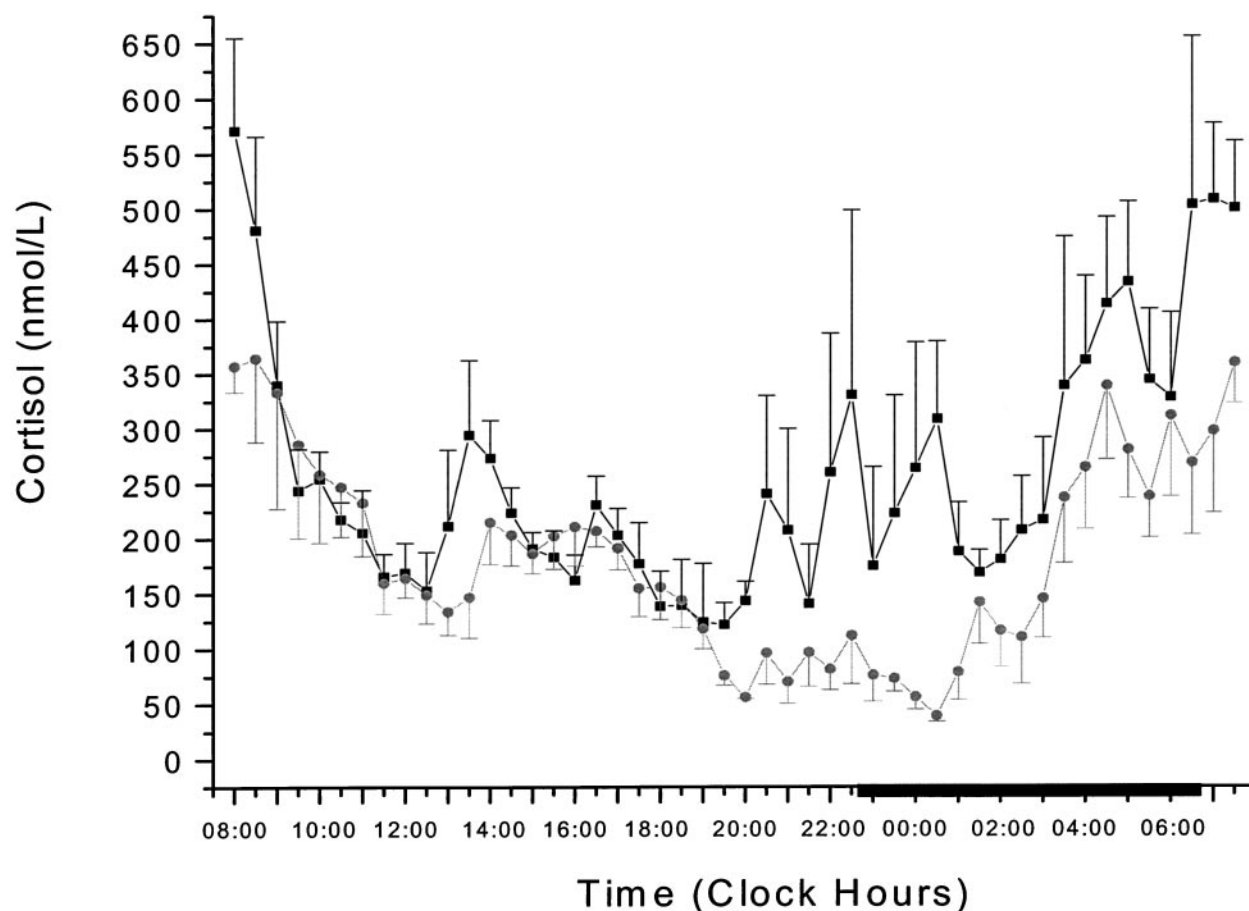


FIG. 4. Twenty-four-hour plasma cortisol concentrations in insomniacs, with low total ST (■) vs. those with high total ST (○) (MANOVA). The thick black line indicates the sleep recording period. The error bar indicates SE. *, $P < 0.01$.

hypertension, coronary artery disease, and stroke. Our study suggests that, because of their hypercortisolism, chronic insomniacs are at risk for significant medical morbidity, including hypertension, visceral obesity (with its associated metabolic syndrome), osteoporosis, and others (35).

We have previously suggested that sleep laboratory testing is not necessary in the evaluation and diagnosis of most insomniacs and that sleep laboratory measurements are of limited value in distinguishing insomniacs from normal sleepers (36). The findings of this study suggest that although polysomnographic measurements may provide a reliable index of the biological significance and severity of chronic insomnia, they may not be necessary in making the diagnosis in individual patients. Indeed, the use of the sleep laboratory to predict severity of chronic insomnia is costly and impractical, given that other simpler methods, such as actigraphy (37), may provide information that is just as useful to the practicing physician. Larger studies are needed to establish the clinical utility, *i.e.* severity of chronic insomnia, of objective measures of ST.

Insomnia is a difficult disorder to treat, and multiple methods have been proposed. Pharmacologic studies have reported improvement of sleep indices only on a short-term basis (1), whereas, more recently, it was reported that cognitive-behavioral techniques have a lasting effect in improving the sleep indices of elderly insomniacs (38). However,

there is no clear evidence that improved sleep leads to meaningful changes in daytime well-being or performance (39). Our data suggest that the therapeutic goal in insomnia should not be just to improve the quality or quantity of nighttime sleep. Rather, they suggest that the common practice of prescribing only hypnotics for patients with chronic insomnia, at most, is of limited efficacy. It is possible that medications that down-regulate the activity of the HPA axis, such as antidepressants (40), may be a promising tool in our pharmacologic approaches. The effects of antidepressants on sleep, as well as on the daytime function and well-being of insomniacs, have not been assessed systematically. Preliminary studies have reported improvement of sleep (41, 42). Furthermore, the focus of psychotherapeutic and behavioral modalities, including sleep hygiene measures, should not be to just improve the emotional and physiological state of the insomniac before or during sleep, but rather to decrease the overall emotional and physiologic hyperarousal and its underlying factors, present throughout the 24-h sleep/wake period.

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References

- Kales A, Kales JD 1984 Evaluation and treatment of insomnia. New York: Oxford University Press
- Ford DE, Kamerow DB 1989 Epidemiologic study of sleep disturbances and psychiatric disorders. *JAMA* 262:1479–1484
- American Psychiatric Association 1994 Diagnostic and statistical manual of mental disorders. 4th ed. Washington DC: APA; 551–607
- Buyse DJ, Reynolds III CF, Hauri P, et al. 1994 Interrater agreement for sleep disorders using proposed DSM-IV and ICD-10 diagnoses: a report from the APA/NIMH DSM-IV field trial. *Am J Psychiatry* 151:1351–1360
- Horne J 1988 Why we sleep. New York: Oxford University Press
- Chrousos GP, Gold PW 1992 The concepts of stress and stress system disorders: overview of physical and behavioral homeostasis. *JAMA* 267:1244–1252
- Chrousos GA, Kattah JC, Beck RW, Cleary PA and the Optic Neuritis Study Group 1993 Side effects of glucocorticoid treatment. *JAMA* 269:2110–2112
- Tsuchiyama Y, Uchimura N, Sakamoto T, Maeda H, Kotorii T 1995 Effects of hCRH on sleep and body temperature rhythms. *Psychiatry Clin Neurosci* 49:299–304
- Ehlers C, Reed TK, Henriksen SJ 1986 Effects of corticotropin-releasing factor and growth hormone-releasing factor on sleep and activity in rats. *Neuroendocrinology* 42:467–474
- Opp M, Obál Jr F, Kreuger JM 1989 Corticotropin-releasing factor attenuates interleukin 1-induced sleep and fever in rabbits. *Am J Physiol* 257:R528–R535
- Weitzman ED, Zimmerman JC, Czeisler CA, Ronda J 1983 Cortisol secretion is inhibited during sleep in normal man. *J Clin Endocrinol Metab* 56:352
- Vgontzas AN, Mastorakos G, Bixler EO, Kales A, Gold PW, Chrousos GP 1999 Sleep deprivation effects on the activity of the hypothalamic-pituitary-adrenal and growth axes: potential clinical implications. *Clin Endocrinol (Oxf)* 51:205–215
- Adam K, Tomeny M, Oswald I 1986 Physiological and psychological differences between good and poor sleepers. *J Psychiatr Res* 20:301–316
- Vgontzas AN, Tsigos C, Bixler EO, et al. 1998 Chronic insomnia and activity of the stress system: a preliminary study. *J Psychosomatic Res* 45:21–31
- Rechtschaffen A, Kales A, eds. 1968 A manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects. Bethesda: NIH publication 204
- Yanovski JA, Cutler GB, Chrousos GP, Nieman LK 1993 Corticotropin-releasing hormone stimulation following low-dose dexamethasone administration: a new test to distinguish Cushing's syndrome from pseudo-Cushing's states. *JAMA* 269:2232–2238
- Mojón A, Fernández JR, Hermida RC 1992 Chronolab: an interactive software package for chronobiologic time series analysis written for the Macintosh computer. *Chronobiol Int* 9:403–412
- Fernández JR, Hermida RC 1998 Inferential statistical method for analysis of nonsinusoidal hybrid time series with unequidistant observations. *Chronobiol Int* 15:191–204
- Genazzani AD, Rodbard D 1991 Use of receiver operating characteristic curve to evaluate sensitivity, specificity, and accuracy of methods for detection of peaks in hormone time series. *Acta Endocrinol (Copenh)* 124:295–305
- Rosmond R, Dallman MF, Björntorp P 1998 Stress-related cortisol secretion in men: relationships with abdominal obesity, endocrine, metabolic and hemodynamic abnormalities. *J Clin Endocrinol Metab* 83:1853–1859
- Tan T-L, Kales JD, Kales A, Soldatos CR, Bixler EO 1984 Biopsychobehavioral correlates of insomnia, IV: diagnosis based on DSM-III. *Am J Psychiatry* 141:357–362
- Kales A, Caldwell AB, Prston TA, Healey S, Kales JD 1976 Personality patterns in insomnia. *Arch Gen Psychiatry* 33:1128–1134
- Kales A, Bixler EO, Vela-Bueno A, Cadieux RJ, Soldatos CR, Kales JD 1984 Biopsychobehavioral correlates of insomnia, III: polygraphic findings of sleep difficulty and their relationship to psychopathology. *Int J Neurosci* 23:43–56
- Reynolds 3rd CF, Kupfer DJ, Buysse DJ, Coble PA, Yeager A 1991 Subtyping DSM-III-R primary insomnia: a literature review by the DSM-IV Work Group on Sleep Disorders. *Am J Psychiatry* 148:432–438
- Monroe LJ 1967 Psychological and physiological differences between good and poor sleepers. *J Abnorm Psychol* 72:255–264
- Bonnet MH, Arand DL 1995 24-Hour metabolic rate in insomniacs and matched normal sleepers. *Sleep* 18:581–588
- Stepanski E, Zorick F, Roehrs T, Young D, Roth T 1988 Daytime alertness in patients with chronic insomnia compared with asymptomatic control subjects. *Sleep* 11:54–60
- Bonnet MH, Arand DL 1996 The consequences of a week of insomnia. *Sleep* 19:453–461
- Leprout R, Copinschi G, Buxton O, Van Cauter E 1997 Sleep loss results in an elevation of cortisol levels the next evening. *Sleep* 20:865–870
- Moldofsky H, Lue FA, Davidson JR, Gorczynski R 1989 Effects of sleep deprivation on human immune functions. *FASEB J* 3:1927–1977
- Scheen AJ, Byrne MM, Plat L, Leproult R, Van Cauter E 1997 Relationships between sleep quality and glucose regulation in normal humans. *Am J Physiol* 271:E261–E270
- Brun J, Chamba G, Kihalfallah Y, et al. 1998 Effect of modafinil on plasma melatonin, cortisol and growth hormone rhythms, rectal temperature and performance in healthy subjects during a 36 h sleep deprivation. *J Sleep Res* 7:105–114
- Czeisler CA, Richardson GS 1991 Detection and assessment of insomnia. *Clin Ther* 13:663–679
- Bixler EO, Vgontzas AN, Lin H-M, et al. 2000 Association of hypertension and sleep-disordered breathing. *Arch Intern Med* 160:2289–2295
- Chrousos GP 2000 The role of stress and the hypothalamic-pituitary-adrenal axis in the pathogenesis of the metabolic syndrome: neuro-endocrine and target tissue-related causes. *Int J Obes* 24:S00–S00
- Vgontzas AN, Bixler EO, Kales A, Manfredi RL, Tyson K 1994 Validity and clinical utility of sleep laboratory criteria for insomnia. *Int J Neurosci* 77:11–21
- Jean-Louis G, Zizi F, von Gizycki H, Hauri P 1999 Actigraphic assessment of sleep in insomnia: application of the actigraph data analysis software (ADAS). *Physiol Behav* 65:659–663
- Morin CM, Colecchi CA, Stone J, Sood RK, Brink D 1999 Behavioral and pharmacological therapies for late-life insomnia: a randomized controlled trial. *JAMA* 281:991–999
- Morin CM, Hauri PJ, Espie CA, Spielman AJ, Buysse DJ, Bootzin RR 1999 Nonpharmacologic treatment of chronic insomnia. *Sleep* 22:1134–1156
- Michelson D, Galliven E, Hill L, Demitrack M, Chrousos G, Gold P 1997 Chronic imipramine is associated with diminished hypothalamic-pituitary-adrenal axis responsivity in healthy humans. *J Clin Endocrinol Metab* 82:2601–2606
- Hohagen F, Montero RF, Weiss E, et al. 1994 Treatment of primary insomnia with trimipramine: an alternative to benzodiazepine hypnotics? *Eur Arch Psychiatry Clin Neurosci* 224:65–72
- Hajak G, Rodenbeck A, Adler L, et al. 1996 Nocturnal melatonin secretion and sleep after doxepin administration in chronic primary insomnia. *Pharmacopsychiatry* 29:187–192