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Z. Fang, S. H. Carlson, N. Peng and J. M. Wyss

Am J Physiol Regulatory Integrative Comp Physiol, June 1, 2000; 278 (6): R1490-R1495.

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Aldosterone release during the sleep-wake cycle in humans

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Charloux, Anne, Claude Gronfier, Evelyne Lonsdorfer-Wolf, François Piquard, and Gabrielle Brandenberger. Aldosterone release during the sleep-wake cycle in humans. *Am. J. Physiol.* 276 (*Endocrinol. Metab.* 39): E43–E49, 1999.—The aim of this study was to assess the relative influence on the 24-h aldosterone profile of the adrenocorticotrophic system, primarily modulated by a circadian rhythmicity, and the renin-angiotensin system, which is influenced by sleep. Cortisol, plasma renin activity (PRA), and aldosterone were measured for 24 h in healthy subjects under basal conditions, once with nocturnal sleep and once with a night of sleep deprivation followed by 8 h of daytime sleep. The sleep period displayed high mean aldosterone levels, pulse amplitude, and frequency that were reduced during waking periods. During sleep, aldosterone pulses were mainly related to PRA oscillations, whereas they were mainly associated with cortisol pulses during waking periods. Cross-correlation analysis between sleep electroencephalographic activity in the delta band and aldosterone levels yielded significant results, aldosterone following delta waves by ~30 min. This study demonstrates that the 24-h aldosterone profile is strongly influenced by sleep processes. A dual influence, by the renin-angiotensin system during sleep and by the adrenocorticotrophic system during wakefulness, is exerted on aldosterone pulses throughout the 24-h period.

renin-angiotensin-aldosterone system; adrenocorticotrophic system; circadian rhythm; electroencephalography

ALDOSTERONE, the most potent mineralocorticoid hormone, acts on the collecting duct of the nephron to stimulate sodium reabsorption as well as potassium and hydrogen ion secretion. Aldosterone then plays an important role in regulating electrolyte balance and extracellular fluid volume. Aldosterone secretion has a multifactorial control system. In addition to the long-recognized angiotensin II, adrenocorticotrophic hormone (ACTH), and K^+ , which act by means of a systemic influence, other factors such as atrial natriuretic peptide, vasopressin, vasoactive intestinal peptide, dopamine, and several pituitary peptides have been found to be involved in controlling the function of the zona glomerula (20). Recent investigations revealed that most of them may have an autocrine or paracrine influence on the glomerula cells (10). However, their physiological roles have not yet been determined. The relative influence of angiotensin II, ACTH, and K^+ on aldosterone release in basal conditions is still a subject of debate. This may be due to the complex interactions among the many factors involved in the regulation of

aldosterone secretion. For example, atrial natriuretic peptide decreases aldosterone secretion induced by ACTH or angiotensin II (20). Dopamine either stimulates or inhibits aldosterone secretion induced by angiotensin II (7). The sensitivity of the adrenal cortex to ACTH is increased by splanchnic nerve stimulation (5). Moreover, the magnitude of the aldosterone response to these factors depends on the subject's condition. A reduction of sodium intake increases the adrenal response to angiotensin II as well as the slope of the angiotensin II-aldosterone dose-response curve (16, 17). Results from a study performed on obese subjects suggested that the responsiveness of the renal tubule to the sodium-retaining action of mineralocorticoid hormones is influenced by the metabolic status of the subject (2).

The influences of the two main hormonal systems, i.e., the renin-angiotensin system (RAS) and the adrenocorticotrophic system, on the 24-h profile of aldosterone were studied in the 1970s (1, 8, 11, 12, 14). The authors described an episodic pattern of aldosterone secretion and demonstrated that the major peaks of aldosterone are synchronous with the major peaks of cortisol, which occurred during late sleep and early morning hours. Some of these studies concluded that aldosterone, as well as cortisol, had a circadian rhythmicity (8, 14). However, administration of dexamethasone, which suppresses ACTH secretion, has little effect on aldosterone release (1, 19), suggesting that other systems participate in its control in basal conditions. Most authors found a weak correlation between aldosterone and plasma renin activity (PRA). In these studies, the effect of PRA on aldosterone secretion predominated in sodium-restricted subjects but seemed to be negligible in subjects with normal sodium intake (1, 22). Similarly, in subjects under dexamethasone, changes in aldosterone closely paralleled those of PRA (1). When focus has been on the nighttime secretion, it has been shown more recently that in sodium-restricted subjects aldosterone variations are linked to sleep stages, rapid eye movement (REM) sleep beginning at peak level or in the descending phase of aldosterone oscillations (13). In subjects under basal conditions, however, the relative impact of sleep processes and circadian input on aldosterone release through the RAS and the adrenocorticotrophic system remains unclear.

PRA, measured as an index of renin secretion, and cortisol, which closely reflects ACTH secretion with a 10-min delay, have very different circadian and ultradian patterns. PRA shows oscillations strongly linked to the REM-non-REM (NREM) sleep cycles (3). NREM sleep is linked to increasing PRA, whereas PRA decreases during REM sleep. In subjects with normal sleep structure, administration of drugs that affect

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renin release modulates but does not abolish PRA oscillations (4). In contrast, the 24-h ACTH and cortisol profiles represent models of the circadian rhythm. However, a weak influence of sleep on cortisol secretion has been demonstrated recently, although its modality is still subject to debate (18, 24, 25, 26).

Taking into account the results of the influence of sleep processes on renin and ACTH secretion, we designed this study to determine the relative influence on aldosterone secretion of these two major hormonal control systems, the RAS, the rhythm of which is related to sleep processes, and the adrenocorticotrophic system, which demonstrates primarily circadian rhythmicity. We used an experimental abrupt shift of sleep, which provides a means of determining the respective effects of circadian rhythmicity and sleep processes on 24-h hormonal profiles by removing the masking effect of sleep on the circadian rhythm. The 24-h profiles of aldosterone, PRA, and cortisol obtained under basal conditions with normal night sleep were compared with those obtained after a nighttime sleep deprivation followed by 8-h daytime sleep. PRA, aldosterone, and cortisol were measured simultaneously every 10 min in recumbent subjects under enteral nutrition. Delta wave activity, which reflects sleep deepening, was obtained using the sleep electroencephalogram (EEG) spectral analysis. This technique, which provides a detailed and dynamic description of sleep processes, was used to precisely establish the temporal relationship between sleep structure and aldosterone pulses.

MATERIALS AND METHODS

Subjects. Fifteen healthy Caucasian males aged 21–28 yr participated in this study. They had no medical history, were not taking any medication, and were nonsmokers. They were accepted after medical examination and biological tests as well as questionnaires concerning their usual sleep-wake cycle, behavior, and eveningness-morningness. They gave written informed consent to participate in this study, which has been approved by the Strasbourg Hospital Ethics Committee.

Procedures. The measurements were taken in a soundproof and air-conditioned room equipped for polysomnographic recording and blood sampling. The subjects were habituated to their sleep rooms and experimental conditions on the night preceding the experimental night. The first group of seven subjects was studied in random order with a 1-mo interval, once under the basal condition with normal nocturnal sleep from 2300 to 0700, and once after an acute 8-h delay of the sleep-wake cycle obtained by total sleep deprivation during the night, followed by 8 h of daytime sleep from 0700 to 1500. A catheter was inserted into an antecubital vein 4 h before the beginning of recording and kept patent by a heparinized solution. Continuous enteral nutrition began 6 h before the beginning of blood sampling and was maintained throughout the experiment (Sondalis ISO, Sopharga, Puteaux, France; 110 mg/100 ml sodium, 60 mg/100 ml potassium, 50% carbohydrates, 35% fat, 15% proteins, 378 kJ/h). Supine position was maintained for the duration of the experiment. In these conditions, the normal range of PRA levels lies between 0.1 and 3.0 ng·ml⁻¹·h⁻¹ during waking periods and between 3.0 and 7.0 ng·ml⁻¹·h⁻¹ during sleep. Individual values of sodium and potassium excretion in 24-h urine samples collected the day before the experiment ranged between 106 and 146

meq/day and between 55 and 89 meq/day, respectively. When awake, the subjects listened to music, read, watched television, and conversed with an experimenter to prevent sleep. A second group of eight subjects was studied during a normal nighttime sleep after an habituation night. The catheter was inserted at 1600, a standard meal was given at 1800, and the electrodes were attached at 2100. Sleep recording and blood sampling were performed from 2300 to 0700, subjects being recumbent from 1900 to 0700.

Sleep recording. Recording was based on two EEG derivations (C3 or C4 vs. A2 or A1), one chin electromyogram, and one horizontal electrooculogram (upper canthus of one eye vs. lower canthus of the other eye). In the first group of seven subjects, sleep stages were scored according to the Rechtschaffen and Kales established criteria. In the second group of eight subjects, the EEG signal was converted from analog to digital with a sampling frequency of 128 Hz. The high-pass filter setting was 0.3 Hz for the EEG signal (12 dB/octave). The output of the amplifiers was low-pass filtered (35 Hz). Subsequently, spectra were computed for consecutive 2-s periods by use of a fast-Fourier transform algorithm. To yield one mean spectrum every 10 min corresponding to the blood-sampling interval, a median filter was applied for all 300 consecutive 2-s periods. The spectral parameter studied was delta relative power (0.5–3.5 Hz).

Blood sampling and hormone assessment. Blood was collected throughout the 24-h experiment in an adjoining room. The blood was removed continuously by use of a peristaltic pump and was sampled at 10-min intervals in tubes containing EDTA-K₂ salt. A maximum of 200 ml was removed during the 24 h, which produced no significant change in hematocrit levels. The samples were immediately centrifuged at 4°C, and the plasma was stored at –25°C.

PRA was measured by radioimmunoassay of angiotensin I generated after incubation of the plasma (commercial kits, Sorin Biomedica, Saluggia, Italy). The intra-assay coefficient of variation (CV) for duplicate samples was 4% for levels between 10 and 20 ng·ml⁻¹·h⁻¹; 6% for levels between 2 and 10 ng·ml⁻¹·h⁻¹; 10% for levels between 1 and 2 ng·ml⁻¹·h⁻¹; and 30% for levels below 1 ng·ml⁻¹·h⁻¹. The detection limit was 0.18 ng·ml⁻¹·h⁻¹. Plasma aldosterone was measured by radioimmunoassay (commercial kits, Diagnostic System, Webster, TX). Intra-assay precision for duplicate samples was 7.5% for aldosterone levels >10 ng/100 ml and 10% for levels <10 ng/100 ml. The limit of sensitivity was 0.5 ng/100 ml. Plasma cortisol was measured by radioimmunoassay (commercial kit, Ciba Corning Diagnostics, Cergy Pontoise, France). The detection limit was 0.2 µg/dl. The intra-assay CV for duplicate samples assayed was 4% for levels >6 µg/dl and 10% for levels <6 µg/dl. All of the samples from one subject were measured in the same assay to avoid interassay variations.

Analysis. The pulse analysis program ULTRA (23) was used for quantitative detection and characterization of PRA, cortisol, and aldosterone oscillations. This program takes into account the limit of detection of the analytic procedure and the precision of the assay for various ranges of concentrations. The threshold was three times the CV. For each significant oscillation (e.g., if both the increase and the decrease were significant), the ascending portion, the declining portion, the total duration, and the absolute increment were calculated.

A two-way ANOVA for repeated measurements with Greenhouse-Geisser correction and a bilateral *t*-test with Bonferroni procedure for multiple comparisons were used to assess the statistical differences between the mean plasma levels, the mean number and absolute amplitude of the peaks, and the percentages of concomitant or orphan peaks. Two conditions,

nighttime sleep and daytime sleep, and three periods, 2300–0700, 0700–1500, 1500–2300, were considered.

For each subject, the proportion of aldosterone pulses potentially induced by the RAS or the adrenocorticotrophic system was calculated. We defined four types of temporal associations between aldosterone and PRA or cortisol: 1) aldosterone pulses coincident with PRA oscillations alone, 2) aldosterone pulses coincident with cortisol pulses alone, 3) aldosterone pulses coincident with both PRA and cortisol pulses, 4) aldosterone pulses coincident with neither PRA nor cortisol pulses (“orphan” aldosterone pulses). Because ACTH pulses precede cortisol secretion by 10 min, aldosterone pulses were considered to be coincident with cortisol pulses when cortisol pulses occurred in a time window of three sampling points, -1 , 0 , and $+1$. Aldosterone pulses were considered to be coincident with PRA oscillations when PRA oscillations occurred in a time window of three sampling points, -2 , -1 , and 0 .

The temporal relationships between aldosterone plasma levels, PRA, and cortisol plasma levels were quantified using cross-correlation analyses (Box Jenkins Time Series Analysis, BMDP Statistical Software). Analysis was performed from sleep onset to awakening for nighttime sleep as well as for daytime sleep. A second cross-correlation analysis was performed between plasma aldosterone levels, PRA or cortisol plasma levels, and EEG delta relative power. For aldosterone, PRA, and cortisol, an estimation of the slow trend was determined by adjusting a least squared polynome to the series of data. The polynomial values were subtracted point by point from the series of hormonal levels. For the cortisol-delta activity relationship, the analysis started with the onset of the first significant cortisol pulse. Cross-correlation coefficients were computed for lags -4 to $+4$ between two chronological series, each lag corresponding to a 10-min interval. The highest of these nine cross-correlation coefficients was taken into account for each individual.

RESULTS

Sleep quality. Sleep efficiency (total sleep duration/total recording duration) did not differ between the nighttime-sleep condition and the daytime-sleep condi-

tion (0.86 ± 0.04 vs. 0.81 ± 0.03 , $P < 0.4$). The proportions of slow-wave sleep (slow-wave sleep duration/total sleep duration, %) and of REM sleep (REM sleep duration/total sleep duration, %) were similar in normal nocturnal and shifted daytime sleep ($16 \pm 1\%$ vs. $19 \pm 2\%$, $P < 0.3$; $20 \pm 2\%$ vs. $20 \pm 2\%$, $P = 1$, respectively).

Twenty-four-hour hormonal profiles. Figure 1 illustrates the 24-h profiles of plasma aldosterone levels in one representative subject with normal nighttime sleep from 2300 to 0700 (*top*) and with shifted daytime sleep from 0700 to 1500 after a nighttime sleep deprivation (*bottom*). During normal nighttime sleep, aldosterone pulses were significantly amplified compared with the subsequent waking period. After the shift in the sleep period, a sleep-associated increase in pulse amplitude was clearly apparent during the daytime hours.

The mean 24-h profiles of plasma aldosterone, PRA, and cortisol are represented in Fig. 2. In the normal nighttime sleep condition, the mean aldosterone levels were significantly higher during the 2300–0700 and the 0700–1500 periods than during the 1500–2300 period [$+213\%$ ($P \leq 0.03$) and $+194\%$ ($P \leq 0.04$) of the levels recorded during the 1500–2300 period, respectively; Table 1]. Awakening at 0700 was followed by some large aldosterone pulses that paralleled those of cortisol (Fig. 2). In the daytime sleep condition, aldosterone levels were higher during the 0700–1500 sleep period than during the two 8-h waking periods ($+186\%$, $P \leq 0.003$). During both nighttime and daytime sleep, a significant increase in PRA levels [$+143\%$ during nighttime sleep ($P \leq 0.04$) and $+325\%$ during daytime sleep ($P \leq 0.001$)] was observed compared with the waking periods. In contrast, cortisol showed significantly higher levels between 0700 and 1500 than during the preceding 2300–0700 period in both experimental conditions because of its diurnal rhythm [$+210\%$ in the nighttime

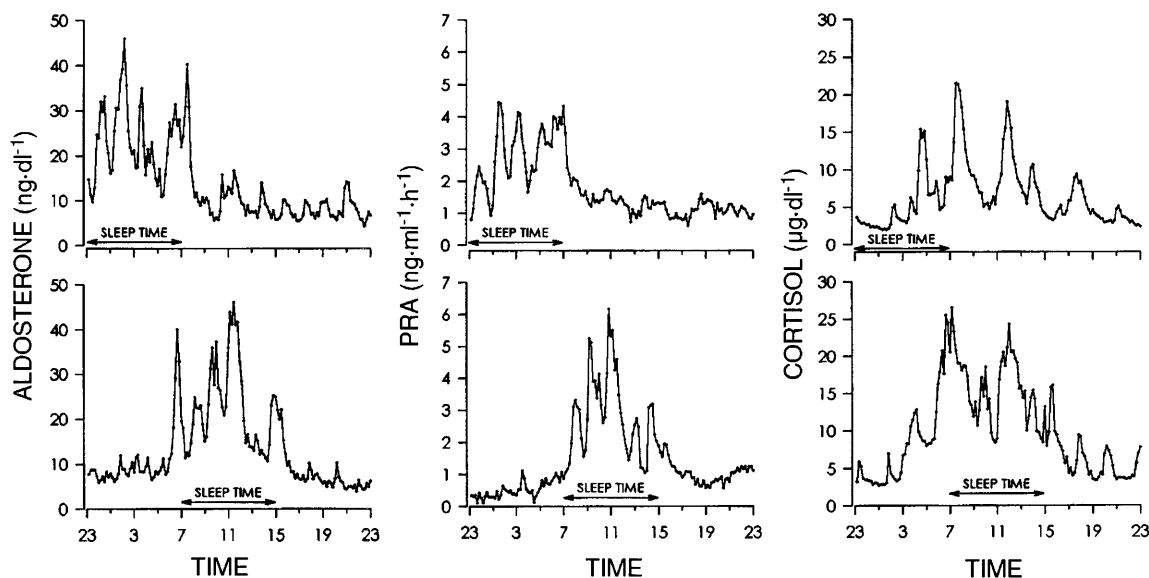


Fig. 1. Twenty-four-hour profiles of plasma aldosterone levels, plasma renin activity (PRA), and plasma cortisol levels in a representative subject with normal nighttime sleep (*top*) and shifted daytime sleep (*bottom*).

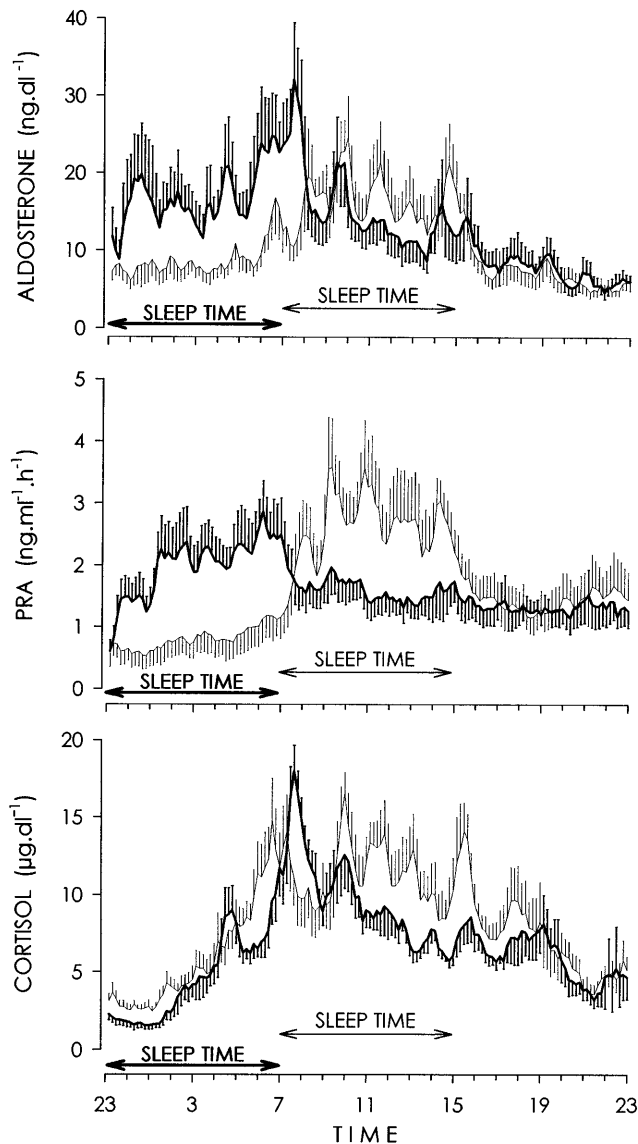


Fig. 2. Effect of an 8-h shift in sleep period cycle on 24-h profiles (means \pm SE) of plasma aldosterone levels, PRA, and plasma cortisol levels in 7 subjects.

sleep condition ($P \leq 0.002$) and +190% in the daytime sleep condition ($P \leq 0.01$).

During nighttime sleep, the number of aldosterone pulses was similar to the number of the subsequent waking period (0700–1500) and higher than during the 1500–2300 period ($P \leq 0.005$; Table 1). After the shift of the sleep period, an increased number of aldosterone pulses was observed during daytime sleep ($P \leq 0.002$). As previously described for PRA, the number of pulses significantly increased during sleep, whenever it occurred. The number of cortisol pulses was not affected by either the condition or the period.

For aldosterone, the pulse amplitude of the normal sleep period (2300–0700) and the subsequent waking period (0700–1500) was higher than that of the 1500–2300 period ($P \leq 0.003$ and $P \leq 0.004$, respectively; Table 1). In the daytime sleep condition, the amplitude of the aldosterone pulses was significantly enhanced during the sleep period ($P \leq 0.03$). During sleep, the amplitude of PRA pulses was significantly enhanced whatever the condition ($P \leq 0.04$ during nighttime sleep, $P \leq 0.001$ during daytime sleep). In contrast, the amplitude of cortisol pulses did not vary significantly according to the condition or the period.

Coincidence between aldosterone, PRA, and cortisol pulses. The following results emerged from the rather complicated data that are summarized in Table 2. During the sleep periods in both conditions, most aldosterone pulses were preceded by PRA oscillations (64% during nighttime sleep, 40% during daytime sleep, $P \leq 0.16$), whereas 16% of aldosterone pulses during nighttime sleep and 48% of aldosterone pulses during daytime sleep were preceded by both PRA and cortisol pulses. Only 10% of aldosterone pulses were concomitant with cortisol pulses alone during these sleep periods. In contrast, during the waking periods, aldosterone pulses were most often concomitant with cortisol pulses (37–88% depending on the waking period). Less than 23% of aldosterone pulses were preceded by PRA oscillations, and few of these were preceded by both PRA and cortisol pulses (0–16%). Orphan aldosterone pulses, i.e., those not preceded by

Table 1. Effect of an 8-h shift in sleep period on plasma levels, number of pulses, and absolute amplitude of pulses of aldosterone, PRA, and cortisol

	Nighttime Sleep			Daytime Sleep		
	2300–0700	0700–1500	1500–2300	2300–0700	0700–1500	1500–2300
Plasma levels						
Aldosterone, ng/100 ml	16.8 \pm 4.1	15.3 \pm 3.1	7.9 \pm 1.5	8.8 \pm 1.4	16.4 \pm 2.8	7.3 \pm 1.2
PRA, ng \cdot ml \cdot h ⁻¹	2.0 \pm 0.4	1.3 \pm 0.3	1.2 \pm 0.3	0.8 \pm 0.3	2.6 \pm 0.5	1.5 \pm 0.4
Cortisol, µg/dl	4.6 \pm 0.3	9.7 \pm 0.7	6.1 \pm 0.9	5.9 \pm 0.5	11.2 \pm 1.3	7.2 \pm 0.8
Pulse number						
Aldosterone	4.1 \pm 0.3	3.9 \pm 0.4	3.1 \pm 0.3	2.6 \pm 0.4	4.1 \pm 0.7	2.5 \pm 0.3
PRA	4.0 \pm 0.2	1.9 \pm 0.3	1.7 \pm 0.2	0.9 \pm 0.1	4.9 \pm 0.5	1.0 \pm 0.4
Cortisol	2.7 \pm 0.6	3.6 \pm 0.4	2.4 \pm 0.5	3.9 \pm 0.7	4.9 \pm 0.5	2.7 \pm 0.2
Pulse amplitude						
Aldosterone, ng/100 ml	15.8 \pm 4.2	11.8 \pm 2.5	5.4 \pm 1.4	8.7 \pm 1.8	15.7 \pm 1.8	5.6 \pm 1.1
PRA, ng \cdot ml \cdot h ⁻¹	1.7 \pm 0.2	1.1 \pm 0.2	1.0 \pm 0.1	0.8 \pm 0.2	2.0 \pm 0.2	0.8 \pm 0.3
Cortisol, µg/dl	6.8 \pm 1.4	8.1 \pm 1.5	5.9 \pm 1.1	6.2 \pm 0.8	8.3 \pm 0.8	7.6 \pm 0.5

Values are means \pm SE of 7 subjects. PRA, plasma renin activity.

Table 2. Proportion of aldosterone pulses concomitant with PRA oscillations, cortisol pulses, and both PRA and cortisol pulses

	Nighttime Sleep			Daytime Sleep		
	2300–0700	0700–1500	1500–2300	2300–0700	0700–1500	1500–2300
PRA/aldosterone	64 ± 9	22 ± 10	20 ± 8	3 ± 3	40 ± 13	23 ± 9
Cortisol/aldosterone	9 ± 4	45 ± 7	37 ± 7	88 ± 9	10 ± 5	51 ± 9
PRA/cortisol/aldosterone	16 ± 6	9 ± 6	10 ± 6	0 ± 0	48 ± 14	0 ± 0
“Orphan” aldosterone	11 ± 5	24 ± 7	33 ± 7	9 ± 6	2 ± 2	27 ± 9

Values are means ± SE of 7 subjects expressed in %. “Orphan” aldosterone pulses were not preceded by either PRA or cortisol pulses.

either PRA or cortisol pulses, were also detected, the lowest proportions being observed during the sleep periods and the highest during the 1500–2300 periods in each condition.

Cross-correlation coefficients between aldosterone and PRA ranged from 0.41 to 0.73 during nighttime sleep and from 0.36 to 0.69 during daytime sleep (Table 3). In most subjects, PRA oscillations preceded aldosterone pulses by 20 min. In contrast, cross-correlation coefficients between cortisol and aldosterone ranged from –0.47 to 0.82, with lags ranging from –3 to +3, indicating that there was no systematic temporal association between cortisol and aldosterone during sleep.

Cross-correlation between delta relative power and aldosterone, PRA, or cortisol. The nocturnal individual aldosterone, PRA, and cortisol profiles were analyzed with regard to the delta relative power during normal nighttime sleep in a second group of eight subjects (Table 4). For aldosterone, the cross-correlation coefficients ranged from 0.24 to 0.62, variations in delta relative power preceding aldosterone pulses by 20–30 min in most subjects (Fig. 3). PRA oscillations were concomitant with or followed delta relative power with a 10-min delay. As previously described (9), for the period of pulsatile cortisol secretion, an inverse relationship was found with delta relative power, cross-correlation coefficients ranging from –0.18 to –0.47. Inverse variations in plasma cortisol levels followed variations in delta relative power by 10–20 min.

Table 3. Cross-correlation coefficients and time lags between plasma aldosterone levels, PRA, and plasma cortisol levels during a normal nighttime sleep and a daytime sleep

Subject No.	Nighttime Sleep				Daytime Sleep			
	PRA/Aldosterone		Cortisol/Aldosterone		PRA/Aldosterone		Cortisol/Aldosterone	
	Lag	r	Lag	r	Lag	r	Lag	r
1	+1	0.72	0	0.71	–1	0.56	+2	–0.16*
2	+2	0.41	+3	–0.47	–2	0.69	–2	0.43
3	+1	0.73	0	0.82	–2	0.69	–2	0.75
4	+3	0.43	–2	0.33	–2	0.50	–2	0.36
5	+2	0.48	0	0.74	–3	0.45	–1	0.55
6	+2	0.61	–2	0.51	–2	0.61	–3	0.46
7	+2	0.68	0	0.70	–1	0.36	–1	0.28*

r, Cross-correlation coefficients. Cross-correlation analysis started with sleep onset. For positive lags, the 1st variable precedes the 2nd one. *Nonsignificant ($P \geq 0.05$).

DISCUSSION

In the present study, using an acute shift in normal sleep, we demonstrate that the 24-h aldosterone profile, generally thought to be entirely driven by the circadian clock, is also strongly influenced by sleep. Sleep processes have a stimulatory effect on aldosterone release, as demonstrated by high mean levels together with high pulse amplitude and pulse frequency observed during the sleep period and reduced levels during sleep deprivation. This pattern of secretion is similar to that of PRA, known to be influenced by sleep, but differs from that of cortisol, an indicator of ACTH secretion, which is under a predominantly circadian influence. The large increase in plasma aldosterone levels and pulse amplitude after awakening from nighttime sleep is attributable to the increase in the activity of the adrenocorticotrophic axis, reflected in the large cortisol pulse at 0700. Cortisol levels remain high during the 0700–1500 period, reflecting circadian influence, which explains high aldosterone levels regardless of whether subjects are sleeping or awake. Thus both the adrenocorticotrophic system and the RAS play a role in creating the aldosterone 24-h rhythm in basal conditions.

The relative influence on aldosterone pulses of both hormonal systems is of particular interest, because it widely differs during sleep and wakefulness. From the complex data presented in this study, it seems that aldosterone pulses were mainly related to PRA oscillations during the sleep periods, whereas aldosterone

Table 4. Cross-correlation coefficients and time lags between plasma aldosterone levels, PRA, plasma cortisol levels, and relative delta power during a normal nighttime sleep

Subject No.	Delta/Aldosterone		Delta/PRA		Delta/Cortisol	
	Lag	r	Lag	r	Lag	r
1	+2	0.48	0	0.29	+1	–0.18*
2	+3	0.47	+1	0.51	+1	–0.42
3	+3	0.52	+1	0.58	+2	–0.30
4	+2	0.62	0	0.47	0	–0.41
5	+3	0.24*	+1	0.28	+2	–0.34
6	+2	0.43	0	0.52	+2	0.28
7	+3	0.32	0	0.65	+3	–0.47
8	–1	0.36	+1	0.32	+2	–0.41

Delta, relative delta power. Cross-correlation analysis started with sleep onset for aldosterone and PRA and with the onset of the 1st significant pulse for cortisol. For positive lags, the 1st variable precedes the 2nd one. *Nonsignificant ($P \geq 0.05$).

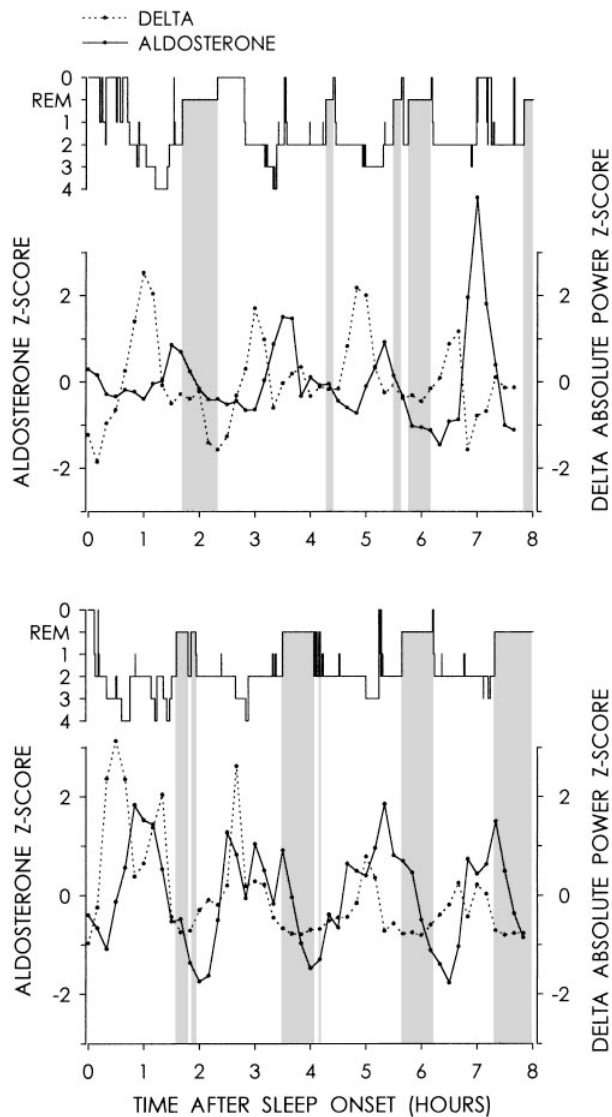


Fig. 3. Concomitant profiles of plasma aldosterone levels and relative delta power after Z-score transformation in 2 representative subjects.

pulses of lower magnitude were mainly associated with cortisol pulses during the waking periods. Indeed, it has been previously demonstrated that if one of the two hormonal systems regulating aldosterone release is depressed, the other will compensate (1, 13). Aldosterone levels during daytime sleep, when both cortisol and PRA pulses were present, were not higher than during nighttime sleep, when cortisol has a quiescent period of secretion. Thus, in basal conditions, it does not seem that the adrenocorticotrophic system and the RAS have any synergic or additive influence on aldosterone release. This also confirms that the two systems seem to operate independently of one another. Thus, in the present study, in subjects under constant conditions (enteral nutrition and continuous bed rest without the influence of repeated meal intake and changes in posture that mask the underlying rhythm), it was found that there is a balance between the RAS and the adrenocorticotrophic system, depending on the sleep-

wake cycle. This phenomenon of interaction appears to be unique and, to our knowledge, such dual control depending on the vigilant state has not been described for any other hormonal system.

Early studies described a pulsatile pattern of aldosterone release and demonstrated that most of the aldosterone pulses are synchronous with those of cortisol, suggesting that aldosterone, like cortisol, is under circadian control (1, 8, 11, 12, 14). A predominant role of PRA on aldosterone release has been described only in sodium-depleted subjects (22). In all these studies, sleep and its possible masking effect on a truly endogenous rhythm have received little attention. In addition, several factors might explain why no relationship could be found between aldosterone and PRA pulses in subjects with a normal sodium diet. In most of these studies, the authors did not analyze the sleep periods and the waking periods separately. Second, in the earliest studies, the frequency of blood sampling (every 20–30 min) was too low to render a precise description of the 90-min oscillatory patterns of these hormones and to detect the relationship between sleep structure and aldosterone release. Finally, the assay used for aldosterone measurements should have had a low specificity and may have cross-reacted with cortisol.

Another argument for the preponderance of the control of RAS is the significant positive correlation observed between aldosterone pulses and variations in delta wave activity. We have previously shown that PRA oscillations systematically parallel changes in delta wave activity, whereas an inverse temporal relationship exists between the pulsatile portion of cortisol release and delta relative power (9, 15). From these results, it can be concluded that an indirect relationship exists between aldosterone pulses and sleep deepening and lightening cycles, aldosterone following PRA oscillations by 10–20 min and delta waves by ~20–30 min. Only a few studies have previously related plasma aldosterone levels to specific sleep stages. Rubin et al. (21) reported that mean aldosterone levels were 24% higher during REM sleep than during all other sleep stages combined. It has also been found that REM sleep usually begins at peak level or in the descending phases of aldosterone pulses (13). The present study, by using spectral analysis of sleep EEG instead of the conventional scoring of sleep stages, offers a more precise picture of the relationship between sleep structure and aldosterone release.

Although modifications in potassium balance can produce changes in aldosterone secretion, previous studies have shown that plasma potassium does not change significantly over the 24-h period, indicating that this factor has little influence on aldosterone pulsatility (1, 13, 22). Many other factors have been reported to be involved in the control of aldosterone secretion, such as atrial natriuretic peptide, vasopressin, insulin, somatostatin, dopamine, serotonin, and vasoactive intestinal peptide (20). Their role in the generation of the aldosterone pulses, especially of the orphan aldosterone pulses that predominantly appear

during the waking period in the late afternoon, deserves further investigation.

A physiological role of the sleep-related oscillations of aldosterone was suggested in a study on patients with obstructive sleep apnea (6). These patients experienced severe sleep fragmentation, disturbed nocturnal PRA and aldosterone profiles, and increased urine excretion during the night. Treatment with continuous positive airway pressure (CPAP) improved sleep, restoring slow-wave sleep and REM sleep and, consequently, PRA and aldosterone oscillations. This increased activity of the renin-angiotensin-aldosterone system combined with a normalized atrial natriuretic peptide secretion, also due to CPAP treatment, lowered the nocturnal urine natriuresis and diuresis of these patients.

In conclusion, the 24-h aldosterone rhythm, generally thought to be purely circadian, is strongly influenced by the sleep-wake cycle. Of the two hormonal systems implicated in aldosterone pulsatility, the adrenocorticotrophic system is operative during wakefulness, whereas the RAS plays a major role during sleep, which contributes to the nocturnal maintenance of water and salt homeostasis.

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