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Ultradian Rhythms in Hydromineral Hormones

Key Words

Sleep
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Abstract

The maintenance of hydromineral homeostasis depends on the coordinated action of arginine vasopressin (AVP), atrial natriuretic peptide (ANP), the renin-angiotensin-aldosterone system and other recently identified endocrine or paracrine hormones. Several reports have pointed out the changes in urinary excretion and osmolality during the sleep-wake cycle and the rapid eye movement (REM)-non(N)REM sleep cycles. No such changes occur for ANP levels which have a flat profile over 24 h. The pulsatile fluctuations of AVP are described as random. The ultradian rhythm of plasma renin activity (PRA) depends on the regularity of the REM-NREM sleep cycles and the nocturnal curves reflect all disturbances in the internal sleep structure. A study with a shift in the normal sleep time clearly demonstrated that both PRA and aldosterone oscillations are sleep-stage dependent. These hormones could account for the ultradian variations in renal function. The nocturnal oscillations in sympathovagal balance may play an additional role. It is suggested that a central generator synchronizes endocrine, renal, autonomic and sleep processes.

The control of sodium and salt metabolism demonstrates a highly integrated series of mechanisms which regulate fluid volume and solute concentration to a remarkable degree. It has been recognized for some time that the maintenance of hydromineral homeostasis depends on the coordinated action of arginine vasopressin (AVP), atrial natriuretic peptide (ANP) and the renin-angiotensin-aldosterone system. New advances have taken place over the last few years. The role of brain, heart and of various endocrine organs has been emphasized. New peptides with natriuretic, diuretic and vasoactive properties have been discovered, which act as endocrine and paracrine hormones at all levels of the circulation. The link between the pivotal role of the kidney and of

extrarenal systems is still being assessed but new data support an important role for these peptides in cardiovascular homeostasis.

In recent years, ultradian rhythms with period averaging 90-100 min have been identified for some of the hormones regulating the fluid-electrolyte metabolism. This cycle length is of particular significance since it corresponds to the length of the rapid eye movement (REM)-non(N)REM sleep cycles and has also been observed in various physiological and behavioral processes. The present report reviews current knowledge of the ultradian rhythms in renal function and in the potential controlling endocrine systems and evokes the role of the autonomic nervous system in relation to the kidney function.

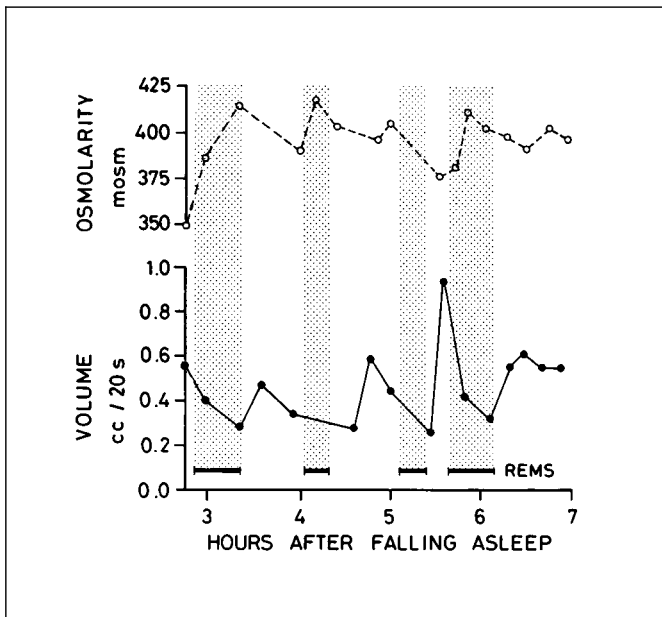


Fig. 1. Simultaneous plot of urine volume and osmolarity, and REM-state epoch during a typical nocturnal sleep [adapted from 3].

Diuresis and Natriuresis

The circadian variations in urine excretion have been well documented. In man, during normal sleep-wake cycle, urine flow and electrolyte excretion are higher during the day than during the night [1]. Circadian rhythmicities in urine constituents persist under constant conditions, suggesting a control by the circadian clock. They can be reversed in subjects sleeping habitually in the daytime. However, some dissociations between electrolyte rhythms have been observed in humans living in the absence of environmental time cues [2] which suggests that the 24-hour variations in urine constituents are not only regulated by the circadian oscillator.

In contrast to the large number of human studies on urinary circadian rhythmicity, relatively few studies have investigated ultradian rhythms in renal function in humans. In searching for changes in physiological parameters associated with REM sleep, Mandell et al. [3] described ultradian variations in urinary excretion of sleeping patients (fig. 1). Urine flow decreased and osmolarity increased every 90 min, coinciding with REM sleep. Similar ultradian rhythms in urine flow and electrolyte concentrations were later demonstrated in waking subjects who consumed a constant amount of fluid and urinated every 10 min [4]. During daytime too, the ultradian

rhythm in urine flow was clearly out of phase with electrolyte and osmolality rhythms. These data suggest that important mechanisms from the endocrine systems and the central nervous system control the regulation of sodium and of water homeostasis both during sleep and wakefulness.

Arginine Vasopressin

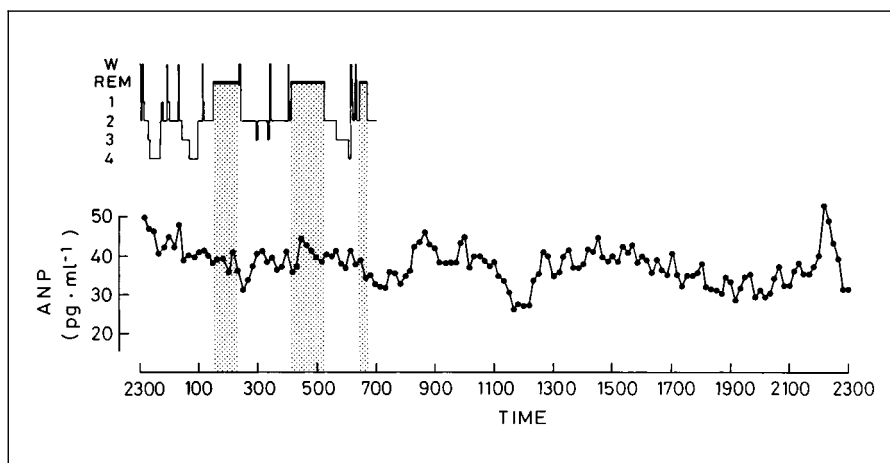
AVP which controls free water clearance of the kidney through its action on the convoluted tubules, plays an important role in maintaining hydromineral homeostasis. The release of AVP from the posterior pituitary is controlled by two main factors of physiological importance, plasma osmolality and the effective circulating blood volume or blood pressure. The release of appropriate amounts of AVP in response to changes in plasma osmolality and in blood volume or pressure is mediated by the combined effects of various excitatory and inhibitory inputs to the magnocellular neurons of the supraoptic and paraventricular nuclei in the hypothalamus.

Due to the lack of sensitivity of radioimmunoassay for human AVP, the studies tempting to establish an ultradian rhythm are scarce. Rubin et al. [5] described random fluctuations in AVP, unrelated to changes in osmolality and unrelated to specific sleep stages. This result was extended by Lavie et al. [6] who observed in awake subjects that AVP secretion is episodic but that the secretory episodes are not temporally related to the cycles in urine flow. It has been hypothesized that the cyclic changes in urine flow may be under the control of hormones other than AVP.

Atrial Natriuretic Peptide

A prodigious effort has been made in the last few years to understand ANP involvement in fluid and electrolyte homeostasis. This peptide, isolated from human atrial tissue, has natriuretic, diuretic and vasorelaxant properties. It is released by atrial distension, in response to blood volume expansion and during changes in dietary sodium intake. Plasma levels are increased in pathophysiological conditions such as cardiac and renal failure. It is well known that ANP inhibits aldosterone secretion directly and reduces renal renin release. ANP blocks specifically the vasoconstrictor actions of angiotensin II and possibly that of AVP. Many of the original studies employed pharmacological doses of the peptide, however recent reports

Fig. 2. Individual plasma ANP profile during a normal 24-hour sleep-wave cycle and the corresponding sleep stage pattern. REM sleep phases lie within the shaded areas [from 9].



have confirmed that elevations in plasma ANP above the physiological range produce similar effects.

The existence of a circadian rhythm in the plasma concentration of ANP is still matter of controversy. A diurnal variation in plasma ANP has been described in some studies in young healthy volunteers and in hypertensive patients [7], whereas it has been found to be age-dependent in hospitalized elderly subjects [8]. The time of ANP peak values differed greatly between the studies, probably due to variable experimental conditions (posture, activity, diet, blood sampling). In supine subjects studied during a normal sleep-wake cycle under continuous enteral nutrition with 10-min blood sampling, we found that mean ANP levels did not differ significantly throughout the 24-hour period [9]. ANP levels were similar both during the sleep periods and the periods spent awake. Fluctuations, often of small amplitude, were observed around this mean without any defined periodicity and without any temporal relationship with specific sleep stages or intra-sleep waking periods (fig. 2).

The Renin-Angiotensin-Aldosterone System

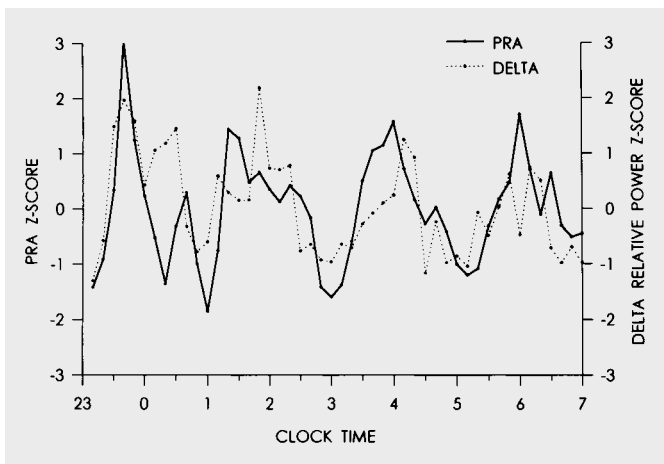
One system of pivotal importance to the appropriate regulation of sodium balance and extracellular fluid volume is the renin-angiotensin system. Renin activation is a major component of the homeostatic responses that maximize sodium conservation and maintain blood pressure and extracellular fluid volume. It is well recognized that complex interactions exist among the multiple factors regulating renin release. Reviews that have been concerned with tentative classification pointed out the major role of

the macula densa mechanism, of the baroreceptor mechanism and of the sympathetic nervous system.

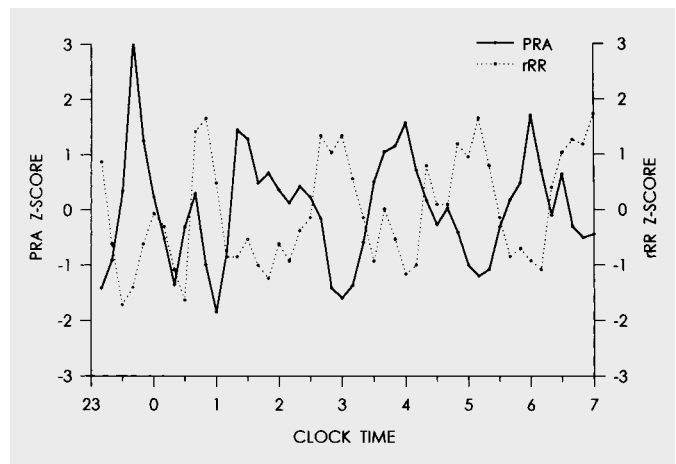
There is also evidence that the central nervous system participates in controlling renin release. In this respect, the finding in humans of a 90–100 min ultradian rhythm in plasma renin activity (PRA) strongly linked to the REM-NREM sleep cycles is of particular interest [10]. This association cannot be broken. Intervening factors which stimulate renin release do not affect this relationship [11] and in case of sleep disorders, such as sleep apnea [12], narcolepsy [13], sleeping sickness [14], renin variations reflect all disturbances in the sleep structure of the patients.

More recently, we examined the association between nocturnal PRA oscillations and sleep electroencephalographic (EEG) activity, as assessed by spectral analysis [15]. We found that delta wave activity and PRA levels paralleled each other in all individuals (fig. 3). An increase in slow wave activity was associated with an increase in PRA, whereas a decrease in slow wave activity was associated with a decrease in PRA.

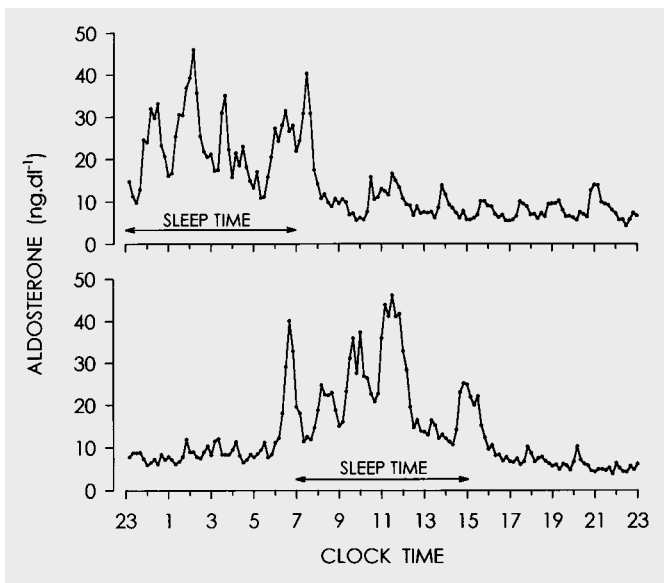
A study using a shift in the sleep time clearly demonstrated that renin release increased during sleep whenever it occurs [16]. Aldosterone, which is under the control of potassium, of adrenocorticotrophic hormone (ACTH) and of the renin-angiotensin system, had higher mean levels during the sleep period, and clearly reflected the increased renin release (fig. 4). During sleep, individual curves showed large oscillations which did not exist in awake subjects. These results demonstrate that the 24-hour aldosterone variations are not circadian in nature but are related to sleep processes through the stimulatory effect of the renin-angiotensin system.



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Fig. 3. Concomitant profiles of PRA and of delta relative power after Z-score transformation. Ascending phases indicate sleep deepening; descending phases indicate sleep lightening.

Fig. 4. Effect of an 8-hour delay of the sleep-wake cycle on 24-hour plasma aldosterone profiles in a subject who had regular NREM-REM sleep cycles during nighttime sleep (top) and during daytime sleep (bottom).

Fig. 5. Opposite variations of PRA and complex heart rate variability as assessed by interbeat autocorrelation coefficient of RR intervals (rRR) after Z-score transformation.

One model for examining the physiological action of these hormones is represented by sleep apnea patients who have fragmented sleep, increased urine and sodium excretion, increased ANP release and decreased activity of the renin-angiotensin-aldosterone system. The treatment with nasal positive airways pressure immediately restores the sleep cycles, diminishes ANP levels and restores the nocturnal oscillations in renin and aldosterone which contribute to normalize urine and sodium output [17].

The Sympathetic Nervous System

It is not completely clear if the renal sympathetic nerves are essential for renal function. However, it has been established that they can influence sodium excretion, urine flow, renal blood flow, glomerular filtration rate and renin release. Because renal sympathetic outflow is under central control, the modulation of renal nerve activity is important in the control of water and salt balance. We have investigated the sympathovagal balance using complex heart rate variability, as assessed by interbeat autocorrelation coefficients of RR intervals (rRR) [18]. During sleep, oscillations in rRR and in PRA levels were found to be inversely related with significant ($p < 0.05$) cross-correlation coefficients. Oscillations in auto-

onomic balance preceded pulses in delta wave activity and the associated renin release by about 10 min (fig. 5). These results suggest that the relationship between the activity of the autonomic system and renin release which is normally stimulated by sympathetic nerve activity could reverse during sleep. They raise the question of the common processes that give the intermittent signal for concomitant increases in slow wave activity and in renin release from the kidney.

To conclude, the different aspects of the role played by fluid regulatory hormones in the generation of ultradian

oscillations of urine and salt excretion have been investigated. Among the multiple endocrine and paracrine factors involved in fluid homeostasis, hormones from the renin-angiotensin system could account for the ultradian variations in renal function. The nocturnal oscillations in sympathovagal balance may play an additional role. It is tempting to propose that common central mechanisms regulate EEG activity, hormone release and renal function, but future work should be directed towards a further understanding of the coordinated action of the different pulse generators.

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