Sleep pattern in an experimental model of chronic kidney disease

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Hirotsu C, Tufik S, Bergamaschi CT, Tenorio NM, Araujo P, Andersen ML. Sleep pattern in an experimental model of chronic kidney disease. Am J Physiol Renal Physiol 299: F1379–F1388, 2010. First published September 8, 2010; doi:10.1152/ajprenal.00118.2010.—The prevalence of sleep disorders is significantly elevated in chronic kidney disease (CKD) patients. Numerous factors likely contribute to the high prevalence of sleep problems in uremic patients. The objective of this study was to evaluate the long-term sleep pattern changes in uremic rats during disease progression. Sleep recordings of the rats were monitored during light and dark periods that lasted 12 h each. These recordings were performed on days 7, 30, 60, and 90 after CKD induction. Cardiovascular, hormonal, and biochemical changes were evaluated at these same time points in control and uremic rats. CKD progression was reflected by the presence of hypertension and progressive increases in urea, creatinine, and cholesterol levels. We also observed hormonal fluctuations of corticosterone and ACTH, which indicated a potential alteration in the hypothalamic-pituitary-adrenal axis in diseased rats. In addition, rats with CKD demonstrated fragmented sleep with a greater number of arousals and decreased sleep efficiency in the light period during disease progression. In the dark period, there was an initial increase in sleep efficiency in CKD rats, but after 90 days of CKD, these animals slept less compared with the control group. Collectively, these metabolic and cardiovascular changes were associated with the persistent alterations in sleep architecture observed in CKD rats.

renal disease; sleep; hypertension; corticosterone; dyslipidemia; electroencephalogram; uremia

CHRONIC KIDNEY DISEASE (CKD) results in profound biochemical changes that affect numerous organs and regulatory systems, such as the central nervous system. Patients with uremic encephalopathy exhibit disorientation, somnolence, and coma symptoms, among others (26). Additional symptoms include anorexia, nausea, vomiting (35), sexual dysfunction (41), depression (29, 30), and sleep disorders (28).

The prevalence of sleep disorders is significantly higher (up to 80%) in patients with chronic renal failure compared with the general population (22). In the predialysis era, uremia was associated with “day-night reversal” as a late symptom (24, 25). Sleep disorders associated with CKD may be related to the effects of uremic toxins on the central nervous system (18) and may result in excessive daytime sleepiness, insomnia, decreased mental acuity, restless legs syndrome, and sleep apnea (23).

Although poor sleep quality is common in patients with CKD, the mechanism responsible for this phenomenon has not been clearly determined. In addition to causing sleep disruption and sleep loss, these conditions may further increase the considerable cardiovascular morbidity and mortality of this patient population (43). Thus sleep abnormalities appear to have significant negative effects on quality of life and functional health status. A more complete understanding of the sleep problems associated with CKD is necessary to improve health outcomes and facilitate research efforts directed at preventing or counteracting CKD-related sleep disorders.

In our laboratory, we have adopted a widely studied experimental model of CKD (5/6 nephrectomy) in rats, in which the associated metabolic and cardiovascular changes closely resemble those observed in humans. These changes include hypertension, progressive renal injury, proteinuria, and nitrosative stress (11, 12, 34, 39, 47). Only one previous study has evaluated sleep disorders in animal models of CKD (28). In that study, an indirect evaluation of the sleep-wake cycle was attained by the punctual measurement of movements using infrared monitoring. However, this method does not permit for the complete scoring of sleep stages, which is essential for an objective assessment of the sleep-wake cycle.

Renal diseases are devastating illnesses that are associated with a high morbidity and mortality, and the incidence of renal failure is growing at a rate of 6–8% per year worldwide (13). Considering that sleep disorders are common in patients with CKD and do not receive the clinical and scientific interest they deserve, it is important to understand the pathogenic mechanisms that govern the initiation and progression of sleep disorders in CKD using animal models. Despite the availability of other animal models, rats and mice remain the main species used by researchers in the fields of nephrology and sleep. Thus the current study was undertaken to characterize the sleep architecture of a rat CKD model during different disease stages to clarify whether the observed sleep pattern mirrors the changes that occur in humans with chronic renal failure. Second, we aimed to analyze the cardiovascular, biochemical, and hormonal alterations that occurred during disease progression and to correlate these alterations with possible changes in the sleep architecture.

MATERIALS AND METHODS

Animals

This study was performed using adult male Wistar rats (250–350 g) that were bred in the animal facility of CEDEME (UNIFESP). The rats were maintained in a temperature-controlled room (23 ± 1°C) with a 12:12-h light-dark cycle (lights on at 7:00 A.M.) and free access to food and water in standard polypropylene cages. All of the procedures used in the present study complied with the Ethical and Practical Principles of the Use of Laboratory Animals (4), and the experimental protocol was approved by the Ethical Committee of UNIFESP (no. 1848/08).
Experimental Protocol

For the cardiovascular and biochemical experiments (Fig. 1A), after disease induction (day 0), the CKD group (n = 46) was distributed into five subgroups according to disease duration: CKD30 (30 days, n = 10), CKD60 (60 days, n = 10), CKD90 (90 days, n = 10), CKD120 (120 days, n = 8), and CKD150 (150 days, n = 8). The control (CTRL) group (n = 15) was simultaneously evaluated at the same time points (3 animals for each time point). For the sleep pattern study (Fig. 1B), after disease induction and electrode implantation (day 0), the CKD group (n = 32) was distributed into four subgroups according to disease duration: CKD7 (7 days, n = 8), CKD30 (30 days, n = 8), CKD60 (60 days, n = 8), and CKD90 (90 days, n = 8). The CTRL group (n = 12) was simultaneously evaluated at the same time points (3 animals for each time point). We elected to interrupt the sleep recording at CKD90 because only a few animals survived after 90 days, and the sleep record quality was compromised.

Induction of CKD

The animals were randomly assigned to either the CTRL or the CKD group. In the CKD model, the right kidney was removed, and an infarction of 2/3 of the left kidney was achieved through the ligation of two of the major branches of the left main renal artery, as described elsewhere (52). The CTRL group did not undergo a mock surgery, but they received anesthesia equivalent to the CKD group. The procedures were conducted under ketamine and xylazine anesthesia (40 mg/kg and 20 mg/kg body wt, respectively, ip) using strict hemostasis and aseptic techniques. After the surgery, both the CTRL and CKD rats received penicillin (20,000 U in 0.1 ml im), sodium diclofenac (25 mg/ml ip), and ibuprofen (50 mg/ml vo). We elected not to perform the mock surgery because of the quick recovery of rats from this procedure, which made this surgery unnecessary and unhelpful for the chronic parameters evaluated in the current study. However, we acknowledge the lack of a sham surgery control as a limitation of this study.

Stereotaxic Surgery

For the sleep pattern protocol, immediately after renal ablation, stereotaxic surgery was performed to implant electrodes and to assess the sleep-wake cycles of the rats. While under deep anesthesia, the rats were mounted in a classical stereotaxic frame (Insight Instruments). Two bipolar electrodes with four stainless-steel screws (ø 0.9 mm) were placed in the skull through small holes that had been bored in the right lateral frontoparietal region (1 pair) to monitor the bipolar electrocorticogram (ECoG). Two nickel-chromium flexible wires were inserted in the neck muscles to record the electromyogram (EMG). All of the rats received penicillin (20,000 U in 0.1 ml im), sodium diclofenac (25 mg/ml ip), and ibuprofen (50 mg/ml vo) after surgery. After surgery (5 days), the sockets were connected via flexible recording cables and a commutator to a polygraph and computer. The rats habituated to the apparatus for 2 days, at which point their 24-h acute sleep-wake states (7 days after the CKD induction surgery) were recorded. The sleep-wake records were performed at 7, 30, 60, and 90 days after the surgery in the different subgroups.

Sleep Recording

The recordings were performed on a Nihon Koden (TYO) model QP-223A apparatus using three channels for each animal. The ECoG signals were amplified and filtered with a low-pass filter at 0.5 Hz and a higher cut-off of 35 Hz because the EEG frequency band between 0.5 and 30 Hz has the most clinical relevance in the conscious state. The EMG activity was filtered with a low-pass filter at 5.3 Hz because this allows for the recording of the fast range of frequencies (1, 3, 49, 50 51). Sleep recordings were monitored during light and dark periods that lasted 12 h each and were evaluated on days 7, 30, 60, and 90 after the CKD induction or assignment to the CTRL group. During the experimental period, the rats were maintained in their own cage inside a Faraday chamber. The ECoG traces were visually and manually identified and scored according to Timo-Iaria et al. (53). The follow-

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**A Cardiovascular and Biochemical Protocol**

<table>
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<th>Day 150</th>
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<tr>
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<td>Anesthesia and analgesic CTRL, n=3</td>
<td>Anesthesia and analgesic CTRL, n=3</td>
<td>Anesthesia and analgesic CTRL, n=3</td>
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**B Sleep Pattern Protocol**

<table>
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<th>Day 83</th>
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<td>Nephrectomy 5/6 + Stereotaxic surgery CKD60, n=8</td>
<td>Nephrectomy 5/6 + Stereotaxic surgery CKD30, n=8</td>
<td>Nephrectomy 5/6 + Stereotaxic surgery CKD7, n=8</td>
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</tr>
<tr>
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<td>Stereotaxic surgery CTRL, n=3</td>
<td>Stereotaxic surgery CTRL, n=3</td>
<td></td>
</tr>
<tr>
<td>CTRL group, n=12</td>
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Fig. 1. Experimental protocol. Time lines for the cardiovascular and biochemical protocol (A) and the sleep pattern protocol (B) are shown. CTRL, control animals; CKD, chronic kidney disease animals; MAP, mean arterial pressure acquisition; HR, heart rate acquisition.
Sleep parameters were assessed: sleep efficiency (the total sleep time percentage during the recording time), slow-wave sleep (the deep sleep time percentage throughout the recording), paradoxical sleep [the sleep stage also called rapid-eye movement (REM) sleep, which presents an EEG pattern similar to waking, despite muscle atonia], and arousals (events with a duration of at least 15 s and comprising an abrupt modification of the baseline ECoG frequency and the high-amplitude EMG activity followed by slow-wave sleep, expressed as absolute numbers).

**Clinical and Cardiovascular Evaluations**

The clinical and cardiovascular data included body weight, heart rate (HR), and mean arterial pressure (MAP), which were measured in subgroups CKD30, CKD60, CKD90, CKD120, and CKD150 and their respective CTRL groups. After the disease induction period, all of the animals were anesthetized with halothane (2%) using an anesthesia vaporizer. While the rats were breathing spontaneously, we inserted a femoral arterial catheter constructed from PE-50 and PE-10 tubing and filled with saline for the MAP and HR recordings. After surgery, the rats were placed in their home cages to recover for 2 h. The experiments were performed using conscious animals.

**Blood Samples for Biochemical and Hormonal Evaluations**

After the invasive measurement of blood pressure (1 day), animals from each group were killed by decapitation with minimum discomfort between 9:00 and 11:00 A.M. Three rats from the CTRL group were decapitated each day together with those from the CKD groups. Blood was collected in glass tubes and centrifuged to obtain serum or plasma samples. Renal function and lipid profiles were assessed by measuring the concentrations of serum urea, creatinine, sodium and potassium electrolytes, triglyceride, total cholesterol, and fractions using an automated colorimetric method (ADVIA 1650; BAYER Diagnostics) (5, 7). Hormonal profiles were evaluated based on plasma corticosterone and ACTH levels (6). Corticosterone concentrations were assayed with a double-antibody radioimmunoassay method using a commercial kit that is specific for rats (MP Biomedicals). The sensitivity of the assay was 0.25 ng/ml. The ACTH concentrations were determined according to a sequential chemiluminescence immunometric method using a monoclonal murine antibody that is specific for ACTH (DPC Immulite). The sensitivity of the assay was 5 pg/ml.

**Statistical Methods**

Data are expressed as means ± SD. To analyze the parametric data, the Kruskal-Wallis test followed by the Games-Howell post hoc test was used. A correlation analysis (Spearman’s coefficient) was used for the univariate analysis of data from the sleep recording experiment [CTRL (n = 8) and CKD (n = 32) rats that had undergone MAP measurements and blood collection for biochemical and hormonal analysis]. After the correlation analysis, a multiple linear regression was applied to identify the possible determinants of sleep disorders. All variables with a significance of at least 0.01 in the univariate analysis (correlation analysis) were included in the multiple linear regression model. The level of statistical significance was set at P < 0.05.

**RESULTS**

**Body Weight**

A significant weight gain was observed in both groups from the fourth time point onward (P < 0.05). A decrease in body weight was detected in the CKD group compared with the CTRL during only the 2nd and 18th weeks of evaluation (Fig. 2).

**MAP and HR**

The Kruskal-Wallis test revealed (P < 0.001) an increase in the MAP in all of the CKD groups compared with CTRL (P < 0.05) (Fig. 3A). An analysis of the HR values using the Kruskal-Wallis test also revealed significant differences among the groups (P < 0.0001); an increase in HR was observed only...
in CKD30 and CKD150 compared with CTRL (P < 0.05) (Fig. 3B). Despite the significant differences, the HR values determined for all of the groups were within the normal range, which indicated an absence of tachycardia.

**Renal Function**

The Kruskal-Wallis test revealed (P < 0.0001) an increase in serum urea concentrations in CKD90, CKD120, and CKD150 compared with CTRL (P < 0.01) (Fig. 4A). Significant differences in serum creatinine concentrations were also determined among the groups (P < 0.0001); an increase was detected in CKD90, CKD120, and CKD150 compared with CTRL (P < 0.05). A significant difference in the serum creatinine concentration was also observed between CKD30 and CKD150 (P < 0.05) (Fig. 4B). Between-group differences in serum concentrations of sodium (Fig. 4C) and potassium (Fig. 4D) were not statistically significant (P > 0.05).

**Lipid Profile**

The analysis of the triglyceride concentration by one-way ANOVA revealed a group effect (P < 0.001); triglyceride levels were increased in CKD90 compared with all other groups (P < 0.05) (Fig. 5A). Total cholesterol was analyzed by the Kruskal-Wallis test, which revealed significant differences among the groups (P < 0.0001); a significant increase was observed in CKD60 to CKD150 compared with CTRL (P < 0.05). The CKD90 and CKD120 groups also differed from CKD30 (P < 0.01), and groups CKD30 to CKD120 differed statistically from CKD150 (P < 0.01) (Fig. 5B). One-way ANOVA revealed a group effect (P < 0.001); a significant increase in high-density lipoprotein (HDL) cholesterol was observed in groups CKD60 to CKD150 compared with CTRL (P < 0.001). CKD30 and CKD90 also differed statistically from CKD120 (P < 0.001), and CKD150 differed from CKD30, CKD60, and CKD90 (P < 0.001) (Fig. 5C). Our analysis of low-density lipoprotein (LDL) cholesterol concentrations (Fig. 5D) revealed significant between-group differences that were similar to those determined for total cholesterol (P < 0.0001). A progressive increase in LDL cholesterol was found in groups CKD60 to CKD150 compared with CTRL (P < 0.01). Furthermore, CKD90 and CKD120 differed from CKD30 (P < 0.05), and CKD150 was significantly different from all of the other CKD groups (P < 0.01).

**Hormonal Dosage**

The analysis of plasma ACTH (Fig. 6A) using the Kruskal-Wallis test revealed significant differences among the groups (P < 0.0001); significant increases were detected in CKD30, CKD60, CKD90, and CKD150 compared with CTRL (P < 0.05). The concentrations of ACTH in CKD90 and CKD120 were significantly lower compared with those in CKD60 (P < 0.05). The concentration of corticosterone (Fig. 6B) exhibited a group effect (P < 0.0001); only CKD90 demonstrated a difference compared with CTRL (P < 0.05).

**Sleep Parameters**

**Light period. SLEEP EFFICIENCY.** The Kruskal-Wallis test revealed significant differences among the groups (P < 0.0001); we observed a decrease in sleep efficiency in CKD30, CKD60, and CKD90 compared with CTRL (P < 0.05) (Fig. 7A).

**AROUSALS.** One-way ANOVA revealed a group effect (P < 0.0001); there were a greater number of arousals in all of the CKD groups compared with CTRL (P < 0.01) (Fig. 7B).

**PARADOXICAL SLEEP.** A group effect (P < 0.0001) was observed in the increased percentage of paradoxical sleep in
CKD7 compared with CTRL ($P < 0.05$) (Fig. 7C). Moreover, an increase was detected in CKD7, CKD30, and CKD90 compared with CKD60 ($P < 0.05$) (Fig. 7D).

**WAKING.** The Kruskal-Wallis test revealed differences among the groups ($P < 0.0001$); the percentage of time awake was increased in CKD30, CKD60, and CKD90 compared with CTRL ($P < 0.05$) (Fig. 7E).

**Dark period. SLEEP EFFICIENCY.** A group effect ($P < 0.0001$) was found in the decreased percentage of slow-wave sleep in CKD7, CKD30, and CKD90 compared with CKD60 ($P < 0.05$). In addition, CKD30 and CKD90 differed significantly from both CKD7 and CKD60 ($P < 0.01$) (Fig. 8A).

**AROUSALS.** No significant differences were observed among the groups (Fig. 8B).

**PARADOXICAL SLEEP.** A group effect ($P < 0.0001$) was detected in the increased percentage of paradoxical sleep in CKD7 and CKD30 compared with CTRL ($P < 0.01$). Moreover, a decrease was found in CKD60 and CKD90 compared with both CKD7 and CKD30 ($P < 0.05$) (Fig. 8C).

**SLOW-WAVE SLEEP.** A group effect ($P < 0.0001$) was observed in the decreased percentage of slow-wave sleep only in CKD7 and CKD30 compared with CTRL ($P < 0.01$). An increase in slow-wave sleep was found in CKD60 and CKD90 compared with both CKD7 and CKD30 ($P < 0.05$) (Fig. 8D).

**WAKING.** A group effect ($P < 0.0001$) was observed in the percentage of time awake in CKD7, CKD60, and CKD90, which differed statistically from CTRL ($P < 0.05$). A decrease in the percentage of time awake was also determined in CKD7 and CKD60 compared with CKD30 ($P < 0.05$). CKD90 differed statistically from CKD7, CKD30, and CKD60 ($P < 0.01$) (Fig. 8E).

Fig. 6. Hormonal parameters. Blood ACTH (A) and corticosterone (B) concentrations in CTRL and CKD groups at different disease time points. Values are expressed as means ± SD. *$P < 0.05$ compared with CTRL. ¥$P < 0.05$ compared with CKD90 and CKD120.

Fig. 5. Lipid profile. Blood triglycerides (A), total cholesterol (B), high-density lipoprotein (HDL) cholesterol (C), and low-density lipoprotein (LDL) cholesterol (D) concentration in CTRL and CKD groups at different disease time points. Values are expressed as means ± SD. A: *$P < 0.001$ compared with CTRL. #$P < 0.05$ compared with CKD30, CKD60, CKD120, and CKD150. B and D: *$P < 0.05$ compared with CTRL. #$P < 0.05$ compared with CKD30. ¥$P < 0.01$ compared with CKD60, CKD90, and CKD120. C: *$P < 0.001$ compared with CTRL. #$P < 0.001$ compared with CKD30 and CKD90. ¥$P < 0.001$ compared with CKD60.
A negative correlation was observed between the independent variables creatinine, urea, MAP, HR, HDL, LDL, total cholesterol, and ACTH and the dependent variable sleep efficiency (Table 1). In the multiple-regression analysis, only creatinine, urea, and MAP were significant determinants of sleep efficiency, as predictors of diminished sleep quantity (Table 1). A positive correlation was also observed between the independent variables creatinine, urea, MAP, HR, HDL, total cholesterol, and ACTH and the dependent variable number of arousals (Table 2). In the multiple-regression analysis, only MAP was a significant determinant of arousals (Table 2), as a predictor of diminished sleep quality.
Fig. 8. Sleep pattern in dark period. Percentage of sleep efficiency (A), no. of arousals (B), percentage of paradoxical sleep (C), slow-wave sleep (D), and wake (E) during the dark period in CTRL and CKD groups at different disease time points. Values are expressed as means ± SD. A, B, and E: *P < 0.05 compared with CTRL. #P < 0.05 compared with CKD30. ¥P < 0.01 compared with CKD7 and CKD60. C and D: *P < 0.01 compared with CTRL. ¥P < 0.05 compared with CKD7 and CKD30.
Table 1. Spearman’s correlation analysis and linear multiple regression analysis of factors associated with sleep efficiency as the dependent variable

<table>
<thead>
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<td>$r$</td>
<td>$P$</td>
</tr>
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<tr>
<td>Urea, mg/dl</td>
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<tr>
<td>Mean arterial pressure, mmHg</td>
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</tr>
<tr>
<td>Heart rate, beats/min</td>
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<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
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<td>&lt;0.0001</td>
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<tr>
<td>LDL cholesterol, mg/dl</td>
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<td>0.01</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
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<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tryglicerides, mg/dl</td>
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<td>0.121</td>
</tr>
<tr>
<td>Corticosterone, ng/ml</td>
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<td>0.179</td>
</tr>
<tr>
<td>ACTH, pg/ml</td>
<td>-0.568</td>
<td>&lt;0.0001</td>
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HDL, high-density lipoprotein; LDL, low-density lipoprotein.

DISCUSSION

The current study demonstrates the neurophysiological consequences that occur during the progression of CKD and its relationship with cardiovascular and metabolic changes in uremic rats. The results showed that, with a gradual loss of renal function, significant changes occurred in sleep homeostasis, the cardiovascular system (hypertension), the biochemical profile (dyslipidemia), and the endocrine system (hypothalamic-pituitary-adrenal (HPA) activation). Additionally, the study revealed that the renal and cardiovascular impairment contributed initially to the alterations observed in the sleep architecture of CKD animals. Nevertheless, in the long term, the poor sleep quality found in uremic rats led to a sleep-loss condition and might enhance the progression of disease.

The progressive loss of renal function during CKD is associated with nontraditional risk factors such as renal anemia, increase in uremic toxins, and excessive activation of the sympathetic nervous system (SNS), which contribute to an increase in morbidity and mortality (8). As a result of the SNS hyperactivity, the sustained hypertension observed after induction of CKD is the main CKD comorbidity and the main cause of death among renal patients. Moreover, the gradual increase in the concentration of cholesterol in CKD rats is consistent with previous findings concerning the metabolic changes that occur in CKD animal models (10) and in renal patients (48).

CKD rats also presented an increase in plasma ACTH without physiological changes in corticosterone, which indicated a dysfunction of the HPA axis during disease progression. Although most studies have demonstrated HPA axis integrity in patients with renal failure (20, 33), our findings revealed a greater activation of the HPA axis and a high level of stress. Therefore, it is necessary to emphasize that chronic or prolonged stress responses may cause several disease states (45) and contribute to important sleep pattern changes (42). In fact, our results showed that the CKD rats demonstrated poor sleep quality with a progressive decrease in sleep efficiency and an increased number of arousals during the light period, which is the primary sleeping period for rats. These findings corroborate the results of clinical studies demonstrating that CKD patients experience short and fragmented sleep that is associated with a worse quality of life (9, 44). Our results demonstrating the sleep problems that occurred since the beginning of the disease (CKD30) are consistent with the findings of De Santo and colleagues (14, 15), who reported that sleep disorders occur even during the early stages of CKD, when patients do not require therapies such as dialysis or kidney transplantation.

Recently, Barmar and colleagues (9) have demonstrated via actigraphy that CKD and hemodialysis patients demonstrate a decrease in total sleep time and an increase in time awake compared with healthy individuals. However, Parker et al. (44) revealed that hemodialysis patients had a worse sleep quality compared with CKD patients because a decrease in REM sleep was observed only in the hemodialysis patients, suggesting different etiologies for the observed sleep changes in CKD and hemodialysis patients. Similarly, we did not observe marked alterations in REM and slow-wave sleep in CKD rats compared with CTRL. Because the CKD rats slept more during the dark period and slept less in the light period compared with the controls, our results suggest a trend of sleep-wake cycle reversal, which is consistent with clinical data showing evidence of a decreased total sleep time at night and increased symptoms of excessive daytime somnolence in CKD patients (24, 25).

At CKD90, there was an important impairment in the sleep architecture in which a decrease in sleep was observed in both periods. This finding suggests that the end stage of renal disease is accompanied by a significant worsening of sleep and of many other parameters (urea, creatinine, cholesterol). It is important to note that most studies designed to evaluate sleep disorders in CKD patients utilize standardized questionnaires or actigraphy, whereas polysomnography is the gold standard for the appropriate diagnosis of sleep disorders and the assessment of sleep pattern. In this sense, the sleep pattern similarities observed between the disturbed sleep in CKD rats and the data of sleep disorders in patients with CKD demonstrate that the current study can be a reference for this model of sleep architecture in CKD.

The effects of uremic toxins in the central nervous system can mediate the sleep problems associated with CKD (28). Millman et al. (37) noted a slight but significant correlation between sleep apnea syndrome and azotemia. In a more recent prospective study, a strong association between high-efficiency dialysis and fewer sleep disorders was found (54). As a late symptom of predialysis, uremia has been classically associated with sleep-wake cycle reversal (24, 25). Sleep disorders, which appear in ∼80% of patients with chronic uremia, lead to daytime sleepiness, reduced
mental acuity, and a deteriorating quality of life (57). Similarly to our study, Kim et al. (28) demonstrated that animals with CKD exhibit an activity profile reversal. During the disease course, they observed a greater number of movements in CKD rats than in controls, although this behavior was reversed in the dark. However, the absence or presence of movement is neither reliable nor sufficient as a measure of the amount of sleep or the presence of sleep disorders in uremic rats.

Some factors involved in sleep disruption could be the individual peripheral oscillators, which are influenced by the master circadian pacemaker in the suprachiasmatic nucleus. These individual peripheral oscillators are disturbed in CKD patients due to mainly an impaired partial oxygen pressure and blood flow in the kidney (32, 38, 56). For example, some studies have demonstrated that the physiological nocturnal rise in melatonin is absent in hemodialysis patients (27, 31). Because melatonin is an important marker of the circadian timing system (31) and its release can be affected by stress, interacting in this condition with adrenal steroid secretion (46), it is possible that this hormone could also be involved in the sleep disturbances observed in CKD rats. Additionally, circadian rhythms play an important role in the regulation of cardiovascular physiology (21, 40); thus, circadian dysregulation can induce hypertension (19) and renal disease (36).

In addition to melatonin, it has also been suggested that altered cytokine levels have a role in sleep disorders (17). Chronic inflammation, as determined by altered cytokine levels, is highly prevalent in patients with end-stage renal disease (16). Erten et al. (16) have demonstrated an association between sleep complaints and proinflammatory cytokines (IL-1β in particular) in hemodialysis patients. Similarly, we have found an increase in the circulating levels of the proinflammatory cytokines IL-1β, IL-6, and TNF-α in CKD rats (Hirotsu, unpublished data). These cytokines, which are produced by peripheral blood mononuclear cells in the bloodstream, work as pyrogenic signals in specific centers within the central nervous system. Such signals induce the synthesis of prostaglandins, which constitute the central mediators of the coordinated response that leads to a rise in the core body temperature, thus contributing to the circadian disorganization (31).

It is important to stress that the changes observed in the sleep pattern of uremic rats are more than solely a consequence of the disease. They also represent an additional risk factor for CKD exacerbation. Chronically, the establishment of sleep disorders leads to sleep deprivation, which can induce adverse physiological effects, including hypertension, activation of the SNS, impairment of glucose control, and increased inflammation (5). A variety of epidemiological studies have also suggested an association between self-reported sleep duration and long-term health. Individuals who report an increased or a reduced sleep duration have a moderately increased risk for all-cause mortality, cardiovascular disease, and the development of symptomatic diabetes (55). Therefore, sleep is clearly important for a healthy lifestyle in CKD. An adequate sleep duration and quality are important for the normal functioning of daily metabolic and hormonal processes (55) in CKD.

To the best of our knowledge, the overall approach and neurophysiological relationships presented herein have not been reported previously. The multiple linear regression analysis showed that the renal parameters (urea and creatinine) and the hypertension were predictive factors for a worsened sleep quantity and quality. However, it is noteworthy that changes in the HPA axis, HR, and cholesterol were associated with changes in the sleep architecture. Based on these results, it can be inferred that the changes in renal function and blood pressure observed during CKD progression were important factors and contributed to the impaired sleep quality but not via a cause-effect relationship. The modifications of the cardiovascular system, lipid profile, and HPA axis occurred before a significant loss of kidney function, which suggests that the changes in sleep architecture observed after CKD onset may result from the synergistic interaction of many factors inherent to the disease. Similarly, the disrupted sleep pattern in CKD animals becomes an important factor in the exacerbation of renal disease because the chronic condition of poor sleep quality interferes with the body and life as a whole.

Considering that sleep disorders are common in patients with CKD and do not receive extensive clinical and scientific interest, it is important to understand the pathogenic mechanisms that govern the initiation and progression of sleep disorders in CKD. Thus our results highlight the need for a greater consideration of the polysomnography in the clinical follow-up of renal patients to assess and treat potential sleep disorders and thereby improve patient quality of life. Because the disturbed sleep in CKD rats is similar to that observed in patients with CKD, the present study can be a key reference for this new model of sleep disorders in CKD in humans and in mammals.

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REFERENCES


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