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WNK-OSR1/SPAK-NCC signal cascade has circadian rhythm dependent on aldosterone

Koichiro Susa, Eisei Sohara, Kiyoshi Isobe, Motoko Chiga, Tatemitsu Rai, Sei Sasaki, Shinichi Uchida *

Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, 1-5-45 Yushima Bunkyo, Tokyo 113-8519, Japan

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ABSTRACT

Blood pressure and renal salt excretion show circadian rhythms. Recently, it has been clarified that clock genes regulate circadian rhythms of renal transporter expression in the kidney. Since we discovered the WNK-OSR1/SPAK-NaCl cotransporter (NCC) signal cascade, which is important for regulating salt balance and blood pressure, we have sought to determine whether NCC protein expression or phosphorylation shows diurnal rhythms in the mouse kidneys. Male C57BL/6J mice were sacrificed every 4 h (at 20:00, 0:00, 4:00, 8:00, 12:00, and 16:00), and the expression and phosphorylation of WNK4, OSR1, SPAK, and NCC were determined by immunoblot. (Lights were turned on at 8:00, which was the start of the rest period, and turned off at 20:00, which was the start of the active period, since mice are nocturnal.) Although expression levels of each protein did not show diurnal rhythm, the phosphorylation levels of OSR1, SPAK, and NCC were increased around the start of the active period and decreased around the start of the rest period. Oral administration of eplerenone (10 mg/day) attenuated the phosphorylation levels of these proteins and also diminished the diurnal rhythm of NCC phosphorylation. Thus, the activity of the WNK4-OSR1/SPAK-NCC cascade was shown to have a diurnal rhythm in the kidney that may be governed by aldosterone.

1. Introduction

The endogenous circadian clock in mammals is hierarchically organized by molecular oscillators. The central pacemaker is located in the suprachiasmatic nucleus (SCN) of the brain and is entrained by light signals transmitted from the retina through the retinohypothalamic tract [1]. The core clock machinery in peripheral tissues includes clock genes such as Bmal1, Clock, Period (Per1, 2, and 3), and Cryptochrome (Cry1 and 2), which function mainly as transcription factors [2–6]. The central pacemaker in the SCN synchronizes the functions of these peripheral clocks through neuronal and hormonal signaling [7].

The role of circadian rhythms has recently been reviewed for physiological systems including renal functions. Kidneys in healthy human subjects have circadian rhythms for urinary sodium, potassium, and chloride excretion, under which they excrete more electrolytes and produce more urine during daytime than nighttime [6,8]. The daily blood pressure profile also falls during nighttime in healthy subjects and in patients with the dipper pattern of essential hypertension. Essential hypertension in which blood pressure fails to fall during the night (non-dipper pattern) has been associated with more serious target organ damage, such as left ventricular hypertrophy, albuminuria, and cerebrovascular disease, than hypertension with a dipper pattern [9–11]. In addition, it has been shown that blood pressure failed to fall during the night in patients with salt-sensitive essential hypertension [12], and the circadian rhythm of renal sodium excretion was disturbed in the non-dipper type of essential hypertension [13]. Salt restriction and diuretics modify the diurnal variation of blood pressure from a non-dipper to a dipper pattern in salt-sensitive essential hypertension [14,15].

In 2001, mutation in the WNK1 and WNK4 genes was shown to cause pseudohypoaldosteronism type II (PHA II) [16], which is an autosomal dominant disease characterized by hypertension, hyperkalemia, and metabolic acidosis [17]. Since then, the pathophysiological roles of WNK kinases in blood pressure regulation and renal Na and K transport have been investigated [18]. Oxidative stress responsive kinase 1 (OSR1) and Ste20-related proline–alanine-rich kinase (SPAK), which were already known to be serine–threonine kinases that phosphorylate and regulate Na–K–2Cl cotransporter 1 (NKCC1) [19], were identified as substrates of WNK kinases [20–22]. We found increased phosphorylation of OSR1 and SPAK at their phosphorylation sites by WNK kinases and increased NCC phosphorylation at phosphorylation sites by OSR1 and SPAK in the WNK4$^{D561A/+}$ knockin mice, a mouse model of human PHAII having a D564A mutation [19]. In addition, we confirmed by analyzing OSR1 and SPAK knockin mice and SPAK

* Corresponding author. Fax: +81 3 5803 5215.
E-mail address: suchida.kid@tmd.ac.jp (S. Uchida).

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knockout mice [23–25] that NCC phosphorylation in the kidney is completely dependent on OSR1 and SPAK kinase activation by WNK kinases, not only in PHAII mice but also in wild-type mice. Furthermore, we have also shown that salt intake regulates this cascade partially through aldosterone [26]. Thus, this novel kinase cascade in the kidney is important for regulating salt balance and blood pressure, and it is suggested to be involved in the onset of salt-sensitive hypertension.

Recently, a number of clock-controlled genes that have been identified in the kidney through either gene expression profiling or candidate gene approaches have been implicated in the diurnal rhythms for urinary electrolyte excretion. WNK4 and NCC transcripts in the distal convoluted tubule, connecting tubule, and cortical collecting duct in the mouse kidney are also reported to show circadian oscillation [27]. However, the function of the WNK-OSR1/SPAK-NCC cascade cannot be evaluated only by the profile of transcription since its phosphorylation status, which plays a key role in the cascade, is not considered. In this study, we sought to determine the diurnal rhythm of the WNK-OSR1/SPAK-NCC signal cascade in the kidney by examining total protein expression and phosphorylation status of the proteins in this cascade.

2. Materials and methods

2.1. Animals

Studies were performed on 8-week-old male C57BL/6J mice that had free access to food and water. They were adapted to a 12-h light/12-h dark cycle. Eplerenone (10 mg/day) was given to mice with mouse chow during the administration period. The immunoblot analysis was performed on kidney homogenate prepared from at least four mice at each time point. The Animal Care and Use Committee of Tokyo Medical and Dental University approved the experiment.

2.2. Immunoblot analysis

Kidneys were dissected from mice. The homogenates of cortex, medulla, and whole kidney without the nuclear fraction (600 g) was prepared to measure the levels of WNK4, OSR1, and SPAK, and the crude membrane fraction (17,000 g) was prepared to measure the levels of NCC. Semi-quantitative immunoblotting was performed as described previously [19]. The relative intensities of immunoblot bands were determined by densitometry with YabGelImage free software. The commercially available primary antibodies used were anti-OSR1 (M09; Abnova, Taipei, Taiwan), anti-SPAK (Cell Signaling Technology, Danvers, MA), anti-total NCC (Chemicon, Billerica, MA), and anti-actin (Cytoskeleton, Denver, CO) antibodies. Other antibodies used were anti-pOSR1(S325)/SPAK(S383) [28] and anti-pNCC (T53, T58, and S71) antibodies [19]. Alkaline-phosphatase-conjugated anti-IgG antibodies (Promega, Madison, WI) and WesternBlue (Promega) were used to detect the signals.

2.3. Measurement of plasma aldosterone concentration

To determine plasma aldosterone concentration (PAC), venous blood from the mice was collected into heparinized tubes. Plasma was immediately separated from blood samples by centrifugation at 8000 rpm for 5 min at 4 °C and stored at −30 °C. PAC was measured by solid-phase RIA by SRL (Tokyo, Japan).

2.4. Statistics

Data are presented as means ± SE. ANOVA and Tukey's test were used to compare the groups.

3. Results

3.1. The diurnal rhythm of phosphorylation status of the WNK-OSR1/SPAK-NCC signal cascade

To clarify whether the WNK-OSR1/SPAK-NCC signal cascade in the kidney has a diurnal rhythm, the protein expression and the phosphorylation status were evaluated by immunoblot analysis. C57BL/6J mice were adapted to a 12-h light/12-h dark cycle (lights on at 8:00 and lights off at 20:00) for 2 weeks. Then, mice in the group were sacrificed every 4 h (at 20:00, 0:00, 4:00, 8:00, 12:00, and 16:00) by cervical dislocation. The left kidney from each mouse was immediately dissected and homogenized. Start of the active period and start of the rest period corresponded to 20:00 and 8:00, respectively, since C57BL/6J mice are nocturnal.

The immunoblot analysis performed on the whole kidney homogenates is shown in Fig. 1A. Densitometry was used to compare the protein expression levels between time points (Fig. 1B). No apparent diurnal changes in the total expression level of each protein (i.e., WNK4, OSR1, SPAK, and NCC) were found. However, the phosphorylation status of OSR1, SPAK and NCC was increased at 20:00 and was significantly decreased at 8:00; there was a 2.1-fold change between the highest and the lowest phosphorylation levels. Diurnal distributions of acrophases of the phosphorylation status generally corresponded to the start of the active period, while those of bathyphases generally corresponded to the start of the rest period.

Considering the heterogeneity of diurnal oscillation in different nephron segments in the kidney, we also performed the immunoblots of total WNK4, OSR1, SPAK, and NCC in the cortex and medulla separately, focusing on 20:00 and 8:00 (Fig. 1C). Even in either cortex or medulla samples, we could not observe apparent changes in the total protein levels of WNK4, OSR1, SPAK, and NCC between 20:00 and 8:00, further supporting the idea that the difference in phosphorylation of each protein might not be caused by its change in total protein level.

3.2. The effect of aldosterone on the diurnal rhythm of the WNK-OSR1/SPAK-NCC signal cascade

The plasma aldosterone concentration (PAC) has circadian fluctuations in humans [29] as well as in rodents [30,31]. In rodents, the PAC is elevated at the end of the inactive phase and falls at the end of the active phase; this pattern is similar to the pattern we observed in the diurnal rhythm of the WNK-OSR1/SPAK-NCC signal cascade. Although the detail of signal transduction from aldosterone to WNK is not known, we previously showed that this cascade is regulated by aldosterone [26,32]. Therefore, we hypothesized that the circadian fluctuations of PAC could be an upstream regulator for the diurnal rhythm of the WNK-OSR1/SPAK-NCC cascade. To examine this hypothesis, we investigated whether inhibition of aldosterone by eplerenone affected the diurnal rhythm of this kinase cascade in the kidney.

The C57BL/6J mice were divided into two groups, the control group and the eplerenone group. All mice were sacrificed at 20:00 (beginning of active period) or 8:00 (beginning of rest period) by cervical dislocation after adaptation to a 12-h light/12-h dark cycle for 2 weeks. Eplerenone (10 mg/day) was administered to the mice during the adaptation period.

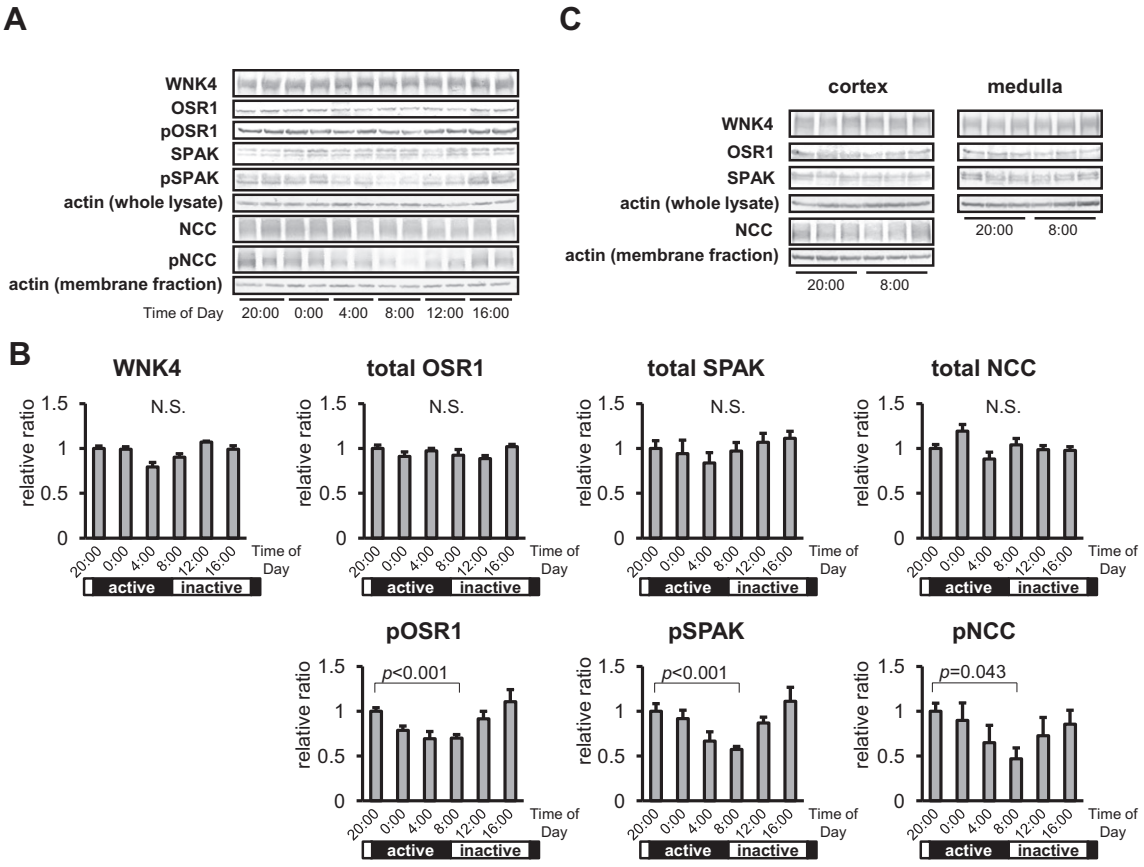

Fig. 1. The diurnal rhythm of phosphorylation status of the WNK-OSR1/SPAK-NCC signal cascade in the kidneys of C57BL/6J mice. (A) Representative immunoblots of WNK4, OSR1, phosphorylated OSR1, SPAK, phosphorylated SPAK, NCC, and phosphorylated NCC in the kidney at each time point. (B) Relative abundance of total and phosphorylated proteins. The total expression level of each protein (WNK4, OSR1, SPAK, and NCC) did not present an apparent diurnal rhythm, whereas phosphorylated OSR1, phosphorylated SPAK, and phosphorylated NCC exhibited acrophase around 20:00 and bathyphase around 8:00. N.S., not significantly different. (C) The total expression levels of WNK4, OSR1, SPAK, and NCC in the kidney cortex and medulla at 20:00 and 8:00. They did not show significant difference between 20:00 and 8:00 in the cortex and medulla. Immunoblot of NCC in the medulla is not shown since NCC was not detected in the medulla.

In our experiments, the PAC of the control group at 20:00 was significantly higher than that at 8:00 (349.50 ± 61.28 pg/ml at 20:00 and 179.40 ± 40.20 pg/ml at 8:00, $n = 12$, $p = 0.031$), which was consistent with previous studies [30,31]. On the other hand, the PAC of the eplerenone group at 20:00 and 8:00 was elevated to 1270.0 ± 64.9 pg/ml and 1337.5 ± 58.6 pg/ml, respectively ($p = 0.469$). These values were markedly higher than the corresponding values in the control group and indicated that the diurnal change in PAC was lost in the eplerenone group.

The immunoblot analysis of NCC and phosphorylated NCC in kidney homogenates is presented in Fig. 2. In the eplerenone group, the phosphorylation of NCC was decreased both at 20:00 and 8:00 as compared to the control group, and its diurnal fluctuation was remarkably decreased. The ratio of the phosphorylation status of NCC at 20:00 to that at 8:00 in the control group was 2.1, whereas the ratio in the eplerenone group was 1.1.

4. Discussion

The central pacemaker in the SCN functions autonomously but is reset each day by light signal. The strict scientific definition of circadian rhythm is a process that exhibits a 24-h pattern of oscillation under constant condition in the absence of timing cues. Therefore, we used the term "diurnal" instead of "circadian" in this study to describe the data obtained in the animal experiments because the animals were entrained on 12-h light–dark cycles.

What is the physiological role of the diurnal rhythm of the WNK-OSR1/SPAK-NCC signal cascade? Blood pressure and sodium excretion of humans increase during the daytime and decrease during the nighttime [33]. Considering this fact, one possible interpretation of our data would be that the WNK-OSR1/SPAK-NCC signal cascade may start to be suppressed upon awakening to prepare for adequate sodium excretion during the day. After adequate sodium excretion, this cascade may start to accelerate at bedtime to decrease sodium excretion during the night.

In this respect, we hypothesized that dysregulation of this cascade might cause hypertension with a non-dipping pattern, since volume expansion by dysregulated salt excretion is the major cause of this type of hypertension [34]. Although there have been no clear reports as to whether PHAII patients have non-dipping hypertension, the hypertension of PHAII patients is salt-sensitive and can be turned to normotensive by sodium restriction or diuretics [17]. In addition, polymorphisms of WNK genes are associated with essential hypertension in the general population [35–37]. Although the pathophysiological roles of these polymorphisms are not clear, these findings suggest that some cases of essential hypertension with a non-dipping pattern might be caused by dysregulation of this cascade. To confirm this hypothesis, it is necessary to establish methods to evaluate the activity of this cascade in patients. Quantification of urinary excretion of phosphorylated NCC could be a candidate marker to estimate the activity of this cascade in human patients.

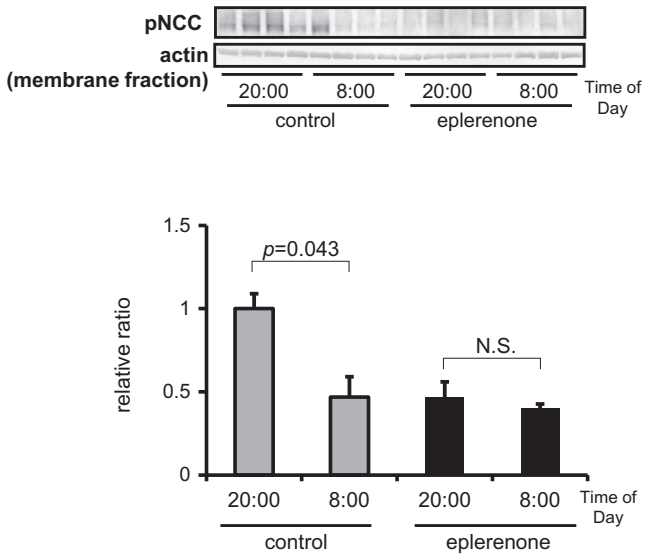

Fig. 2. The effect of aldosterone on the diurnal rhythm of the WNK-OSR1/SPAK-NCC signal cascade. The immunoblot analysis of NCC and phosphorylated NCC in the control group and the eplerenone group at 20:00 and 8:00 is exhibited. The graph shows a comparison of the immunoblot band densities of phosphorylated NCC. In the eplerenone group, the phosphorylation status of NCC was decreased both at 20:00 and at 8:00, and its diurnal rhythm was remarkably diminished. The ratio of the phosphorylation level of NCC at 20:00 to that at 8:00 in the control group was 2.1, whereas the ratio in the eplerenone group was 1.1. N.S., not significantly different.

Na–H exchanger (NHE3), epithelial sodium channel (ENaC) and Na–K–2Cl cotransporter 2 (NKCC2) also play major roles for sodium reabsorption in the kidney [38]. Nishinaga showed by real-time PCR that the level of NHE3 mRNA in the thin descending limbs and thick ascending limbs had a circadian rhythm with a peak at the rise time [39], which is similar to the diurnal rhythm of the WNK-OSR1/SPAK-NCC cascade. Furthermore, Gumz showed by real-time PCR that the expression of ENaC in the inner medullas, outer medullas, and cortex was increased around rise time and decreased around bedtime [40]. Zuber also showed similar results in microdissected distal tubules and collecting duct segments by microarray analysis [27]. These results indicate that the circadian rhythm of expression of NHE3 and ENaC is parallel to that of the WNK-OSR1/SPAK-NCC cascade. Since the regulation of NHE3 and ENaC is also highly dependent on aldosterone [41,42], NCC, NHE3, and ENaC may be involved in the circadian regulation of Na reabsorption as effectors of aldosterone in the kidney. On the other hand, the expression of NKCC2 in distal tubules was shown to have an acrophase around bedtime by the same microarray analysis. Since the distal tubules are not the main site of NKCC2 expression [43], these data do not necessarily exclude the involvement of NKCC2 in the coordinated regulation with NCC, NHE3, and ENaC. It may be necessary to study the circadian rhythm of NKCC2 expression in the thick ascending limb.

Although NCC transcripts had an acrophase around rise time in Zuber's microarray analysis [27], we did not observe a diurnal rhythm in the protein level of NCC by immunoblot analysis. Rather, we found that the level of NCC phosphorylation showed a diurnal rhythm. Phosphorylation is an important regulator of NCC activity and its plasma membrane localization [19] and could be a rapid way of regulating protein function since it does not require protein synthesis. In this respect, it may be reasonable to conclude that the diurnal rhythm of NCC activity was regulated not by its protein level but by its phosphorylation level. In this regard, mechanism(s) of circadian regulation of the WNK-OSR1/SPAK-NCC cascade may be different from those of NHE3 and ENaC. Both the NHE3 and ENaC genes contain E-box-binding elements (CANNTG) in their promoters [44,45], which are critical for the series of transcription-based feedback loops of clock genes [46]. Since Per1, Per2 and Bmal1 are induced by aldosterone [47], aldosterone might regulate NHE3 and ENaC via these clock genes. In addition, mRNA expression of the alpha subunit of ENaC (αENaC) was shown to be regulated by Per1 [40,44]. The expression of αENaC mRNA was attenuated in the renal medulla of the Per1 knockout mice, and these mice exhibited increased urinary sodium excretion. Furthermore, the circadian pattern of renal αENaC mRNA was dramatically altered in the knockout mice [40]. In contrast to these transcription-mediated regulations of transporters and channels, what we observed in the WNK-OSR1/SPAK-NCC cascade is not a change in the absolute abundance of these components, but the levels of phosphorylation (i.e., the activity of the kinases). Since we previously showed that exogenous aldosterone and spironolactone administration increased and decreased the phosphorylation of OSR1, SPAK and NCC in the kidney, respectively [26], it is certain that aldosterone is an upstream regulator of this cascade. However, we have not yet clarified how the signal from aldosterone to WNK kinases is transmitted. We could observe that the increased phosphorylation of OSR1, SPAK, and NCC by low salt intake, which was spironolactone-sensitive [26], was blunted in the Sgk1 knockout mice [48], suggesting that SGK1 might mediate the signal from aldosterone to WNK kinase. However, the detail of aldosterone action on WNK is still under investigation. Identification of the mechanism will also help to clarify how the activity of WNK-OSR1/SPAK-NCC signal cascade is regulated diurnally.

In summary, the WNK-OSR1/SPAK-NCC cascade has a circadian rhythm, which may regulate the diurnal rhythm of sodium excretion with other sodium transport proteins.

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