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Nephrology Dialysis Transplantation

Full Review

Molecular bases of circadian rhythmicity in renal physiology and pathology

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Keywords: circadian, clock gene, kidney

ABSTRACT

The physiological processes that maintain body homeostasis oscillate during the day. Diurnal changes characterize kidney functions, comprising regulation of hydro-electrolytic and acid-base balance, reabsorption of small solutes and hormone production. Renal physiology is characterized by 24-h periodicity and contributes to circadian variability of blood pressure levels, related as well to nychthemeral changes of sodium sensitivity, physical activity, vascular tone, autonomic function and neurotransmitter release from sympathetic innervations. The circadian rhythmicity of body physiology is driven by central and peripheral biological clockworks and entrained by the geophysical light/dark cycle. Chronodisruption, defined as the mismatch between environmental–social cues and physiological–behavioral patterns, causes internal desynchronization of periodic functions, leading to pathophysiological mechanisms underlying degenerative, immune related, metabolic and neoplastic diseases. In this review we will address the genetic, molecular and anatomical elements that hardwire circadian rhythmicity in renal physiology and subtend disarray of time–dependent changes in renal pathology.

INTRODUCTION

All living things that populate the Earth's surface must cope with unpredictable environmental changes that may alter their ecological niches, as well as with predictable changes related to the geophysical 24-h day causing solar lighting alternation and temperature rise and fall [1]. The earliest forms of life were represented by organisms without spatial boundaries to take apart redox reactions, respiration and nitrogen-fixing activity, which are biochemically unable to coexist, and were in that case separated in the temporal dimension [2]. Above and beyond the compartmentalization of chemically incompatible pathways to different time windows, living forms had to escape harmful photo-oxidative consequences of exposure to the environmental light, caused by absence of extensive ozone layer, preordaining at night light-sensitive reactions, such as

DNA synthesis, to preserve them from the solar ionizing radiation [2, 3]. Life forms manage periodic environmental changes with anticipatory phenomena of physiology and behavior, entrained principally by the light/dark cycle and in turn the synchronization of organism functions to the daily alternation of dusk and dawn is critical for maintenance of healthiness and wellbeing. Besides, other factors that powerfully influence timing of biological processes are represented by temperature changes and metabolic flux related to feeding. The neurons of the central nervous system are rather resilient to these stimuli, whereas other organs, such as liver and kidney, are very responsive, so that rescheduling of feeding time or feeding a particular diet disengages metabolic pathways from the light/dark cycle [4, 5]. Body homeostasis relies on the activity of physiological processes that oscillate during the day, among the others those leading to circadian variation of blood pressure levels, related to physical activity, autonomic function and sympathetic innervation, vascular tone, sodium sensitivity [6], as well as renal physiology, characterized by time-related variations of functions including the regulation of hydro-electrolytic and acid–base balance, reabsorption of small solutes, hormone production, vitamin D activation and ultimately blood pressure regulation [7].

The well-timed organization of the array of fluctuations is overridden when behavioral patterns of sleep–wake, rest/activity and fasting/feeding, as well as anabolic/catabolic processes are untimely settled with respect to the natural photoperiod by light exposure at night or shift work. The mismatch between environmental–social cues and physiological–behavioral patterns is defined chronodisruption and leads to internal desynchronization among a number of periodic functions, which may be involved in physiopathological mechanisms underlying degenerative, immune related, metabolic and neoplastic diseases [8].

THE MOLECULAR CLOCKWORK AND THE CIRCADIAN TIMING SYSTEM

The periodicity of biological processes and physiological phenomena is generated by evolutionarily conserved molecular clockworks, ticking autonomously in each cell and working through a transcriptional/translational feedback loop operated by a set of genes and their encoded proteins [9] (Figure 1). They are called clock genes and are represented by *CLOCK*, and its paralog *NPAS2*, *ARNTL-2/BMAL1-2*, *PERIOD* (*PER1-3*) and *CRYPTOCHROME* (*CRY1-2*) (Table 1). *CLOCK* and *BMAL1* switch on the positive limb of the loop, encoding the transcription factors CLOCK and BMAL1 that heterodimerize and bind to E-boxes in the promoters of *PER1-3* and *CRY1-2*, which in turn code for proteins that inhibit the transcriptional activity of CLOCK:BMAL1, closing the loop in a near-24-h period (defined circadian, from the latin *circa*, about, and *dies*, day) [10]. CLOCK:BMAL1 heterodimer drives also the expression of genes encoding the nuclear receptors REV-ERBα/β and RORα/γ, which play a key role in the molecular clockwork, driving the expression of BMAL1 in a negative and positive manner, respectively, binding to the same responsive element, and conferring robustness and amplitude of functioning to the biological oscillator [11]. The oscillation of the molecular clock relies also on post-translational modifications of circadian proteins operated by processes of phosphorylation, mediated by casein kinases 1-δ and 1-ε (CK1δ and CK1ε), glycogen synthase kinase 3 β and adenosine monophosphate (AMP) activated kinase (AMPK), ubiquitination mediated by the E3 ubiquitin ligase complex β-TrCP1 and SCF/Fbxl3 ubiquitin ligase complex, and sumoylation by SUMO2/3 [12–14]. Another process is represented by acetylation, which is involved also in epigenetic changes, is mediated by the acetylase activity of CLOCK on BMAL1, and is counteracted by SIRT1, a type III NAD^+-dependent protein/histone deacetylase (HDAC). NAD^+ levels fluctuate according to the circadian rhythmicity of expression of NAMPT/visfatin/PBEF, the rate-limiting enzyme driving the NAD^+ salvage pathway [15]. Besides, SIRT1 and HDAC3 regulate the functioning of the clock gene machinery driving the circadian rhythm of histone deacetylation [16]. At the moment there is uncertainty about the function of the circadian gene *Timeless* (*Tim*), first discovered in *Drosophila melanogaster* and conserved in mammals, which encodes the protein TIM that associates with TIMELESS interacting protein (TIPIN) and regulates DNA replication processes, playing a key role in the DNA replication system [17].

The bHLH transcription factors DEC1 and DEC2 hinder E-box-mediated transcription, repressing/regulating the circadian transcription of numerous core clock genes and clock-controlled genes. On the other hand, *DEC1* and *DEC2* gene transcription is activated by CLOCK:BMAL1 heterodimer, and the encoded DEC proteins show robust circadian rhythmicity, playing a key role in the molecular clockwork [18].

The clock genes drive the expression of clock-controlled genes and tissue-specific output genes that regulate cell, tissue and organ function, and 2–20% of the transcriptome shows circadian rhythmicity, as evidenced by 24-h gene expression profiling. The rhythmic transcription of output genes is mostly regulated by the clock-controlled PAR bZip transcription factors DBP, HLF and TEF [3, 19, 20]. A coherent phase of oscillation among the biological clocks is dictated by the circadian timing system, comprising a central pacemaker in the suprachiasmatic nuclei (SCN), entrained to the light/dark cycle by photic inputs conveyed by the retino-hyoptalamic tract, and driving self-sustained cell-autonomous oscillators in the peripheral tissues through outputs that are neural (autonomic nervous system) and humoral (melatonin, cortisol) [21]. The entrainment of peripheral oscillators to light/dark cycle depends on the direct output conveyed by sympathetic and parasympathetic nerve fibers targeting peripheral tissues, and the light-induced changes in the expression patterns of the clock gene machinery are organ and time-of-day specific [22]. In both diurnal and nocturnal mammals melatonin is synthesized only at night by the pineal gland [23], whose circadian rhythmicity of secretion is driven by the SCN that express high-affinity melatonin receptors, so that the pineal hormone feedbacks on the SCN [24]. RORα has been proposed as candidate nuclear receptor of melatonin, which promotes a time-dependent decrease in its nuclear levels and changes in its
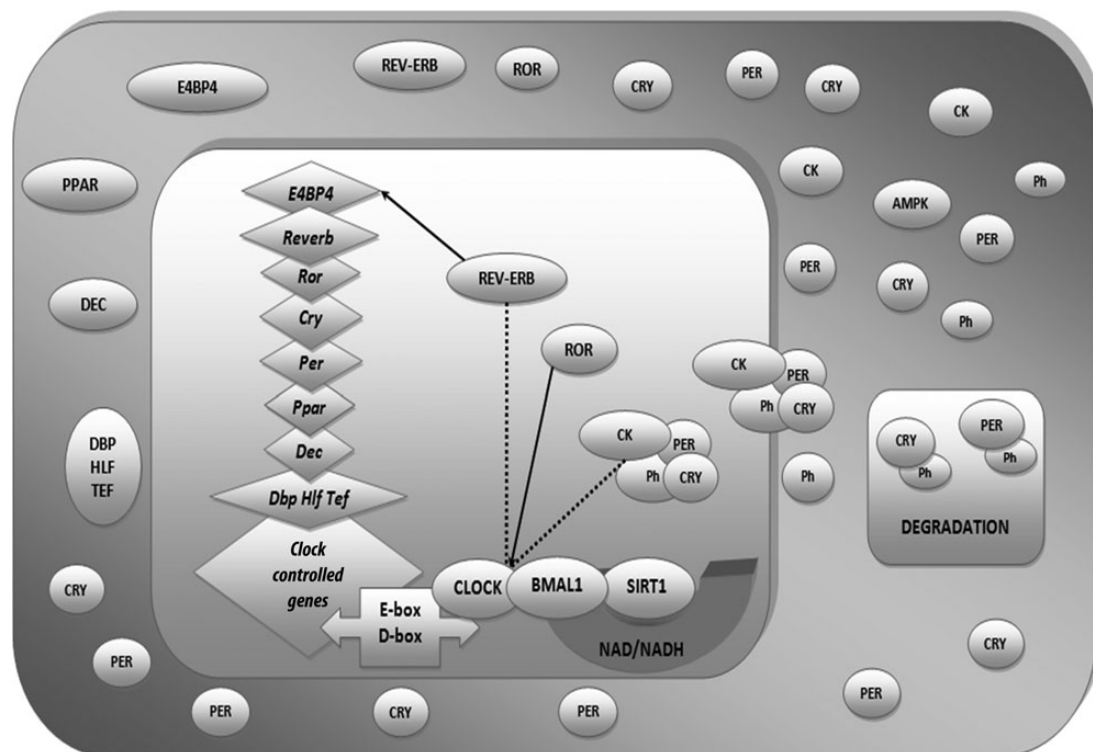
O. Bonny *et al.*

FIGURE 1: Schematic representation of the molecular clockwork. The transcription factors CLOCK and BMAL1 heterodimerize and bind to E-box enhancer elements in the promoters of *PER1-3* and *CRY1-2*, which drive the negative limb in the feedback loop. PER and CRY proteins are phosphorylated (Ph) by casein kinase (CK), translocate back into the nucleus, hampering CLOCK and BMAL1 transcriptional activity. CK and AMP kinase (AMPK) target PER and CRY, respectively, for degradation. CLOCK:BMAL1 heterodimer activates the expression of the nuclear receptor REVERBs, RORs, PPARs, the transcription factors DBP, HLF, TEF, DEC and the clock-controlled genes, which drive cell, tissue and organ functions. An assisting loop is driven by REV-ERBs, which activate E4BP4 transcription and negatively control the rhythmic transcription of BMAL1 impeding RORs binding at the response elements.

transcriptional activity [25]. Regarding cortisol, glucocorticoids bind to GRs and engage genomic glucocorticoid response elements within the core clock gene *PER1*, influencing its transcription and precisely inducing its expression [26].

THE CLOCK GENE MACHINERY IN RENAL PHYSIOLOGY

While partners of the clock gene machinery (including transcription factors BMAL1, CLOCK, PERs, CRYs and REV-ERBs) are ubiquitously expressed and participate in the maintenance of peripheral clock function, their role in specific organs, and more specifically in the kidney, are just starting to be unveiled [27]. In the same way, the mechanism of synchronization between the central and peripheral clocks such as the kidney is still being determined. Neuronal and humoral signals are likely to play a key role [28]. As a key regulator of the circadian clock, the nuclear orphan receptor REV-ERBα has recently been proposed as a synchronizing hinge among the peripheral clocks [29, 30]. Compelling evidence demonstrated that REV-ERBα, alone among the key circadian genes, was expressed in a similar manner with the same peak in expression in several peripheral tissues. Further investigation into the mechanism of REV-ERBα action in the kidney should

contribute to our understanding of clock function in renal tissue.

In the kidney, numerous circadian rhythms are present, including for renal blood flow, glomerular filtration rate and various tubular functions involved in secretion and reabsorption. While these rhythms have been described for decades, it has been difficult to understand the molecular mechanisms that are controlling them, especially in the context of many confounding and interconnected factors, such as hormones or changes in blood pressure for the most obvious ones.

More recently, several attempts to reveal the role of the molecular clock in the kidney have been made, especially by using mouse models in which components of the molecular clock have been knocked out. It should be noted that rodents are nocturnal animals, being active during the night and resting during the day, and this difference should be accounted for when human physiology is considered.

Recent studies involving the kidney shed some light on the regulation of clock gene expression by food and light cues in this tissue. Wu *et al.* [31] looked at the ability of the kidney to reset expression of circadian clock genes following manipulation of the normal circadian rhythm by reversal of the light: dark cycle, reversal of the feeding cycle or a combination of both maneuvers. Reversal of the food cue had a weak synchronizing effect on clock gene expression in the kidney, whereas

Table 1. Non-standard abbreviations and acronyms

CLOCK	Circadian locomotor output cycles kaput
ARNTL-2	Aryl-hydrocarbon receptor nuclear translocator-like
BMAL1-2	Brain and muscle aryl-hydrocarbon receptor nuclear translocator-like
NPAS2	Neuronal PAS domain protein 2
REV-ERBα	Reverse transcript of erythroblastosis gene α
RORα	Retinoic acid-related (RAR) orphan receptor α
β-TrCP1	β-transducin repeat containing protein 1
SCF/Fbxl3	Skp1, Cullin1, F-box and leucine-rich repeat protein 3
NAMPT	Nicotinamide phosphoribosyltransferase
PBEF	Pre-B-cell colony-enhancing factor
bHLH	Basic helix-loop-helix
DEC1	Differentially expressed in chondrocytes protein 1
DEC2	Differentially expressed in chondrocytes protein 2
PAR bZip	Proline- and acid-rich basic region leucine zipper
DBP	Albumin D-site binding protein
HLF	Hepatic leukemia factor
TEF	Thyrotroph embryonic factor
V2R	Receptor to vasopressin
AQP2	Aquaporin-2
AQP4	Aquaporin-4
NHE3	Sodium-proton (Na, H) exchanger
αENaC	Renal epithelial sodium channel
ET-1	Endothelin-1
HKα2	HKα2-containing H,K-ATPase
ERRβ	estrogen-related receptor β
NKCC2	SLC12A1 (sodium/potassium/chloride transporters), member 1
HETE	Hydroxyeicosatetraenoic acid
NCC	SLC12A3 NaCl cotransporter
REN-2	Renin 2
PAI-1	Plasminogen activator inhibitor type 1

reversal of the light:dark cycle affected only *PER1* expression. The combination of light and feeding reversal caused *PER1* and *CLOCK* expression to be shifted by 12 h, suggesting the importance of *PER1* and *CLOCK* to the setting of renal circadian rhythms. A follow-up study looked at the effect of a 30-min feeding stimulus (following 24 h of fasting) on circadian clock gene expression in the heart and kidney [32]. In the heart, mRNA levels of *BMAL1*, *CRY1*, *PER1* and *PER2* were uniformly decreased in animals given the 30-min feeding stimulus, but in the kidney only expression of *PER1* differed significantly from control mice that did not receive a feeding stimulus. These results together suggest that the kidney is less sensitive to feeding cues compared with other tissues and illustrate the importance of alterations in *PER1* levels. Although the kidney appears to be less sensitive to food cues, it is interesting to note that in both studies, the *PER1* gene was the most sensitive to changes in light and feeding cues. These studies were performed using whole kidney RNA samples. Future studies directed at the effects of light and feeding cues on nephron segments or individual epithelial transport mechanisms should be very informative.

Zuber *et al.* [33] addressed the role of the circadian timing system in the distal tubular function by microdissecting the mouse distal convoluted and connecting tubules (DCT–CNT) on the one hand and the cortical collecting ducts (CCD) on the other hand every 4 h for 24 h. Microarray analysis was performed and gene expression profile analysis over 24 h showed that 3814 (DCT–CNT) and 2112 (CCD) genes displayed cyclic changes with an amplitude >1.8-fold. While all genes, taken together, present an acrophase (the peak expression) randomly distributed over 24 h, some categories of genes showed preferential expression at definite time. For instance, the large family of solute carriers (*SLC* family) or the metabolizing enzyme family of cytochrome showed coordinated peak expression at ZT12, the period when the mice start being active and start eating (ZT0 represents the time at which the light is switch on, starting the period of inactivity for mice, while ZT12 is the time at which the light is switched off). This observation indicates that the peak expression of solute transporters and of enzymes needed for metabolizing xenobiotics and nutriments are perfectly synchronized with the time at which the burden of absorbed ions are flooding the kidney and at which needs for enzymatic processes are increased. Another example of coordinated expression of genes acting on the same functional pathway in the kidney is given for water reabsorption. The acrophase of the mRNA expression of *V2R* is perfectly coordinated with the acrophase of the effectors *AQP2* and *AQP4*, and *αENaC* at ZT20. Time-controlled expression of genes involved in a same physiological function, but structurally different, suggests a critical role of the molecular clock in coordinating this function [33]. Anticipation of the work load by increasing the expression of the main effectors ahead of the time at which the load is expected allows a better control, decreases the amplitude of reactivity of feedback loops and strengthens homeostasis. This illustrates the concept of predictive homeostasis as coined by Moore-Ede [34].

Circadian clock-mediated regulation of gene expression in the kidney

Salt preservation implies several transporters and regulatory mechanisms. In the proximal tubule, the majority of transcellular sodium reabsorption is mediated by NHE3, which was

O. Bonny *et al.*

the first renal epithelial transporter to be linked to the molecular clockwork [35] (Figure 2). *NHE3* mRNA and protein expression in the kidney exhibits a circadian pattern, tightly regulated by the clock gene machinery through direct binding of the CLOCK:BMAL1 heterodimer on the E-box of the gene promoter. In particular, *NHE3* peak expression (at a protein level) at ZT16-20 correlates with time at which sodium reabsorption is among the highest. In addition, mice devoid of *CRY1* and *CRY2* are displaying blunted circadian variation of NHE3 expression [35, 36].

Further evidence of the role of the molecular clock in sodium handling was brought forward by Gumz et al. [37]. The expression of the gene *PER1*, one of the transcription factors of the negative limb of the molecular clock, is directly regulated by aldosterone at submicromolar doses. Subsequent studies linked *PER1* to the regulation of the α subunit of αENaC, *in vitro* in models of the collecting duct and *in vivo* in the renal cortex and inner and outer medulla. Inhibition of *PER1* in cell lines issued from the collecting duct and *in vivo* in *PER1*$^{(-/-)}$ mice led to an aldosterone-independent decreased expression of αENaC, the main channel involved in sodium reabsorption in the connecting tubule and CCD. *PER1*$^{(-/-)}$ mice displayed increased urinary sodium loss at steady state, even though the cause is probably not exclusively renal as it would be incompatible with the normal growth of these mice [37, 38].

Using a pharmacological inhibitor of casein kinase 1δ/ε to prevent PER1 nuclear localization, a role for PER1 in the regulation of *ENaC* activity was recently corroborated [39]. A candidate gene approach to identify additional PER1 target genes in renal collecting duct cells showed that PER1 coordinately regulates a set of genes, including *ET-1*, encoding products that function to regulate renal sodium reabsorption [40].

A recent study provided the first evidence that the HKα2 is regulated and functions in a circadian manner [41]. It was shown that *HKα2* mRNA fluctuated with a small amplitude between
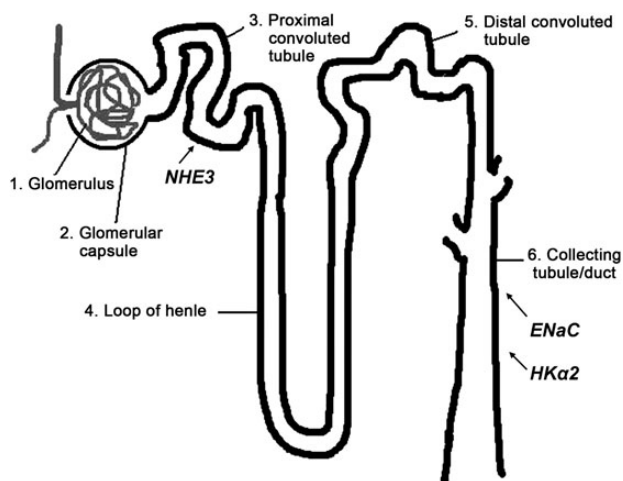

FIGURE 2: The clock-controlled genes driving kidney function in the different segments of the nephron. The genes *NHE3* and *αENaC* are regulated by the core clock proteins at a transcriptional level. An oscillation with a small amplitude between the active and rest phase was evidenced for *HKα2* mRNA in wild-type mice.

the active and rest phase in WT mice. Mice lacking *HKα2* appeared to have a disrupted rhythm of plasma potassium.

It is tempting to speculate that the circadian clock-controlled genes so far identified in the kidney are regulated by the core clock proteins at a transcriptional level. This mechanism of regulation has only been confirmed for *NHE3* [35] and *αENaC* [37]. It is likely that other mechanisms are also involved. One possible mechanism for regulation of renal epithelial transporters is by circadian modulatory nuclear receptors. Crambert et al. recently devised a map of nuclear receptor expression along the nephron by assaying mRNA expression of this gene family in isolated nephron segments [42]. Interestingly, among the most highly expressed nuclear receptors in the whole kidney were REV-ERBα and REV-ERBβ. These two receptors modulate the expression of BMAL1 and likely contribute to the regulation of a myriad of clock target genes. The GR was also expressed along the entire nephron. GR has often been linked to circadian clock function [43] with studies showing a direct interaction between CRY2 and GR [44]. As part of their characterization of nuclear receptor expression along the nephron, Crambert et al. demonstrated that ERRβ was expressed predominantly in the thick ascending limb. Using whole kidney RNA, they showed that ERRβ expression was circadian with a peak of expression at ZT4. Circadian variation was lost in mice lacking a functional *CLOCK* gene. In subsequent *in vitro* studies, this group demonstrated that *in vivo* inhibition of ERRβ resulted in decreased *NKCC2* expression at the mRNA and protein levels [42].

Renal phenotypes in circadian mutant rodent models

In order to address more specifically the role of the molecular clock in renal physiology, mouse models with deletion of transcription factors of the positive limb (CLOCK, BMAL1) or of the negative limb (PERs and CRYs) of the molecular clock were studied. However, due to ubiquitous expression of the components of the molecular clock, the phenotypes of these mice are complex. Indeed, *BMAL1* knockout mice have, for instance, deregulated food behavior and are infertile due to altered testosterone production [45]. Moreover, they present dilated cardiomyopathy [46], a finding consistent with the phenotype reported in mice in which three output genes of the molecular clock (*DBP*, *HLF* and *TEF*) were deleted in a sophisticated triple knockout model and found with cardiac hypertrophy despite low aldosterone and renin levels [47]. This illustrates the variety of phenotypes encountered in these mice and the difficulty of studying the effects of a single component of the molecular clock, such as *BMAL1*, in the kidney of a mouse in which blood pressure, hormone levels and liver metabolism are disturbed. However, and due to the weak expression of *CLOCK* in the suprachiasmatic nucleus, largely replaced by *NPAS2* in this localization, *CLOCK* knockout mice have milder alteration of their feeding behavior, making them a more suitable model for studying peripheral clock function. However, they also become obese and develop full metabolic syndrome over time [48].

CLOCK-deficient mice showed altered water and sodium handling with increased urinary volume, lower urine osmolality, increased hematocrit and increased water consumption

[33]. Altogether, these mice displayed a slight degree of nephrogenic diabetes insipidus. Moreover, these mice exhibited dysregulation of sodium handling resulting in lower blood pressure, with preserved circadian dipping of blood pressure.

Implication of circadian variations of aldosterone levels in the regulation of sodium and blood pressure has been brilliantly demonstrated by Doi *et al.*[49]. They showed that mice devoid of *CRY1/2* have increased blood pressure upon high-salt diet associated with increased aldosterone levels and suppressed renin. They identified the gene *HSD3B6* in mice (human ortholog is *HSD3B1*) as a pivotal enzyme regulating aldosterone synthesis under control of the molecular clock. Thus, suppression of the negative limb of the molecular clock results in increased synthesis of the enzyme HSD3B6, leading to high aldosterone production and salt-sensitive hypertension. Of note, circadian dipping of blood pressure was lost in these mice, a phenotype consistent with the one from *PER2* knockout mice, which harbor attenuated dipping [50]. However, models in which the positive limb of the molecular clock (*BMAL1* or *CLOCK*) was deleted, and the *HLF*, *TEF*, *DBP* triple knockout mouse present low blood pressure, but preserved nocturnal dipping. Altogether, these data show a prominent role of the molecular clock in controlling aldosterone production and, thus, in regulating blood pressure, including nocturnal dipping.

Regarding sodium handling and regulation of blood pressure, another regulatory mechanism has been proposed recently. By comparing renal transcriptomes of *CLOCK*-deficient mice with those of their wild-type littermates, Firsov and his team [51] identified several transcripts involved in arachidonic acid metabolism that are up- or down-regulated in *CLOCK*-deficient mice. These transcripts are coding mainly for cytochrome P450 enzyme family involved in the formation of 20-HETE, a compound that regulates renal sodium reabsorption as well as renal vascular tone, and a powerful mediator of blood pressure control by the kidney. Indeed, 20-HETE content of the kidney is showing circadian rhythmicity, which is shifted in *CLOCK*-knockout mice. Microarray analysis of whole kidney RNA samples isolated every 4 h over a 24-h period demonstrated altered expression of several enzymes in the super-family of cytochrome P450 enzymes. *CLOCK* knockout mice exhibited lower serum levels of 20-HETE over a 24-h period, a finding that was postulated to be a putative mechanism for the lower blood pressure previously observed in mice lacking a functional CLOCK protein. Moreover, renal content and urinary levels of 20-HETE were lower in 24-h collection in *CLOCK* (−/−) mice compared with wild type. Taken together, these results identified CLOCK as an important regulator of arachidonic acid metabolism and as new controller of blood pressure.

Further investigation of renal function and blood pressure in *CLOCK* mutant mice has yielded important clues about the role of this clock gene in the kidney. As previously reviewed [52], Zuber *et al.* [33] demonstrated that *CLOCK* KO mice exhibited lower blood pressure compared with wild-type mice and this phenotype was accompanied by a mild diabetes insipidus. In a follow-up study, Nikolaeava *et al.* [51] extended these findings to show that the circadian rhythm of urinary

sodium excretion was disturbed in *CLOCK* knockout mice. Of note, *CLOCK* knockout mice had a higher urinary Na excretion rate over 24 h compared with wild-type mice.

Interestingly, a recent report [51] showed that *PER1* knockout mice have a similar blood pressure phenotype as the *CLOCK* knockout mice. Indeed, *PER1* knockout mice exhibited a 24-h mean blood pressure that was 18 mmHg less than wild-type mice. *PER1* knockout mice also had elevated levels of inner medullary ET-1 compared with WT mice. Given the known role of ET-1 in mediating the inhibition of ENaC and regulation of blood pressure [53, 54], the observation of increased ET-1 in *PER1* knockout mice provided one possible mechanism that may contribute to the blood pressure phenotype in these mice.

THE CLOCK GENE MACHINERY IN RENAL PATHOLOGY

The alteration of the circadian clock circuitry is responsible for derangement of physiological functions and behavioral patterns, leading to disruption of anatomical integrity and disease onset. On the other hand, inappropriate matching of environmental/social cues and behavioral cycles caused by shift work, jet-lag in transoceanic flight attendants or sleep disturbances, leading to sleep curtailment and mistiming, perturbs the proper temporal organization of biological rhythms and represents a risk factor for a number of diseases.

As mentioned above, casein kinase 1δ/ε regulates nuclear entry of the Period proteins. Tau mutant hamsters have a gain of function mutation in casein kinase Iε and exhibit a decreased circadian period relative to wild-type hamsters. The experimental model represented by a short-period mutation of the circadian system in the hamsters (*Mesocritetus auratus*; *tau*) provides evidence that rhythm disorganization alters cardiovascular and renal integrity [55]. Heterozygous tau mutants have a severe cardio-renal phenotype characterized by cardiomyopathy, hypertrophy with extensive cardiac fibrosis, severely impaired contractility, severe renal disease with proteinuria, tubular dilation and cellular apoptosis, leading to early death [55]. Renal dysfunction was evident as these investigators observed glomerular ischemia, tubular dilation, proteinuria and cellular apoptosis. Removal of the central clock in the SCN led to abolition of the cardiac hypertrophy phenotype in the tau mutants. Interestingly, maintaining the tau mutant hamsters on a shortened light:dark cycle, consistent with their inherent rhythm, resulted in correction of the cardio-renal phenotype and a normal life span [55].

Above and beyond genetic mutations, the functioning of the clock gene machinery in the kidney is influenced by several factors. As reported above, the light and food cues affect the circadian rhythm of the renal clock, but the feeding-induced circadian resetting of the renal clock suggests a weak synchronization effect of the food cue on the renal circadian clock, whereas the re-entrainment of the clock genes is significantly improved after the reversal of both the feeding schedule and the light/dark cycle [31, 32]. On the other hand, daytime restricted feeding significantly altered the expression patterns

O. Bonny *et al.*

of *DEC1* and *DEC2*, inducing circadian expression of *DEC1* with an amplitude of 2-folds after 3 days and 4-folds after 7 days, whereas the expression of *DEC1* but not *DEC2* reverted to being arrhythmic with a reversed feeding schedule coupled with a reversed light/dark cycle. The exogenous injection at certain times of the day of dexamethasone, a glucocorticoid analogue, resulted in rhythmic expression of *DEC1* similar to that seen following 7 days of restricted feeding, suggesting the existence of a glucocorticoid gating mechanism in the circadian expression of *DEC1* in rat kidney [56]. Feeding young adult male BALB/cAn mice with a high-salt diet *ad libitum* for over 2 weeks increased glucose absorption and altered the food entrainment of peripheral biological clocks, advancing the phase of clock gene expression by ~3 h in the liver, kidney, and lung, without changing circadian rhythmicty of feeding, drinking and locomotor activity [57]. Furthermore, male C57BL/6 mice fed a high-fat diet for more or less 1 year to induce obesity, hyperglycemic, hypercholesterolemic and hyperinsulinemic symptoms, showed distorted liver and/or kidney expression of clock genes and clock-controlled genes, suggesting that obesity and metabolic syndrome influence the functioning of the biological clock and the downstream circadian output genes [5].

In rodents and humans, a time-related pattern with day/night changes characterizes micturition frequency, and the circadian rhythmicity is maintained by the genetically encoded biological clock system linking brain, kidney and bladder and controlling urine volume, functional bladder capacity and urodynamics. Mammals urinate less frequently during the sleep/rest period than during the wake/activity period, and this difference is driven by a combination of three factors: decreased arousal level in the brain, decreased urine production rate from the kidneys and increased functional bladder capacity during sleep. The most frequently used animal models, such as rats and mice, are nocturnal animals and show decreased micturition frequency during daytime, and mice with genetically defective circadian clock system show impaired physiological rhythms in these three factors. Similarly, in humans diurnal functional changes in kidney and bladder have been evidenced by several behavioral studies, and in opposition, patients with nocturnal enuresis and nocturia show impairment of these factors. These evidenced pinpoint to a key role played by the circadian clock circuitry and the linkage among the biological clocks in the brain, driving arousal and behavioral patterns, in the kidney, regulating water and electrolyte balance, and in the bladder, controlling output genes such as *connexin 43*, a gene associated with regulation of bladder capacity [58].

The renal biological clock and hypertension

The clock gene machinery plays a key role in the control of blood pressure, driving locomotor activity, metabolic processes, fluid balance and vascular resistance, whose cyclic regulation is driven by the circadian expression of genes encoding enzymes and regulators involved in homeostatic processes at body level and in the kidney [59], while derangements of circadian clock-controlled mechanisms contribute to hypertension onset and maintenance [60]. For example, an important role

in the regulation of salt balance and blood pressure is played by WNK-OSR1/SPAK-NCC signal cascade, which shows circadian rhythms of protein phosphorylation and activity controlled by aldosterone in the kidneys of male C57BL/6J mice [61]. As reported above, in $CLOCK^{(-/-)}$ mice severe derangements of numerous mechanisms, in particular the enzymatic system engaged in the formation of ω-hydroxylated arachidonic acid metabolites, involved in maintaining sodium balance, have been evidenced by renal circadian transcriptome analysis, leading to alteration of the circadian rhythm of renal sodium excretion and plasma aldosterone levels [51]. Besides, altered expression of the clock genes *PER2*, *BMAL1*, *CLOCK* and *DBP* was evidenced in the SCN, rostral ventrolateral medulla, nucleus of the solitary tract, heart and kidney in an animal model of genetic hypertension, the transgenic hypertensive TGR(mREN-2)27 rat, which has the mouse salivary *REN-2* gene integrated into its genome and is characterized by inverse circadian blood pressure profile with fulminant hypertension, unchanged rhythmic pattern of heart rate and increased relative heart weight [62, 63]. As reported above, the simultaneous deletion of all three PAR bZip transcription factors leads to increased morbidity and shortened life span, a cardiorenal alteration associated with a low blood pressure and low aldosterone levels [47], and exhibit significant changes in renal expression of several key regulators of water or sodium balance, leading to a complex phenotype characterized by partial diabetes insipidus, dysregulation of sodium excretion rhythms and a significant decrease in blood pressure [33].

A significant circadian variation has been shown to characterize blood pressure, influenced by a variety of external factors, such as environmental–social cues and by internal factors, such as ethnicity, gender, autonomic nervous system tone, vasoactive hormones, hematologic and renal variables. The time-related profile of blood pressure levels shows a morning increase, a small post-prandial valley and a deeper descent during nocturnal rest, with a 10–20% drop during the night in healthy subjects, whereas patients with secondary hypertension frequently display abnormal circadian blood pressure profiles, characterized by a failure to decrease blood pressure at night [64]. In patients with the salt-sensitive type of hypertension or chronic kidney disease the nighttime drop is not evident, leading to the so-called 'non-dipper' pattern, requiring different ingestion-time-dependent therapeutic strategies, as evidenced by clinically significant dissimilarity with bedtime ingestion in the safety, efficacy, duration of action and/or effects on the 24-h blood pressure pattern of hypertension medications (angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, calcium-channel blockers, α-blockers, β-blockers and diuretics) [65]. Decreased ultrafiltration capacity or enhanced tubular sodium reabsorption causes loss of renal functional reserve and provoke the salt-sensitive type of hypertension. The failing sodium excretory capability leads to nocturnal hypertension, a risk factor for cardiovascular events, which compensates for diminished natriuresis during the daytime and enhances pressure natriuresis during the night, but elevates glomerular capillary pressure leading to glomerular sclerosis and in due course to renal failure [66]. On the other hand, renal function and blood pressure levels

do not seem to influence the circadian rhythm of urinary potassium excretion, which is correlated with that of urinary sodium excretion [67]. Angiotensin receptor blocker treatment increases the urinary sodium excretion during the daytime and reverts the non-dipper blood pressure rhythm into a dipper pattern. Furthermore, the circadian rhythm of urinary potassium excretion is not determined by changes in aldosterone, blood pressure or creatinine clearance, but is determined by the rhythm of urinary sodium excretion during treatment with angiotensin receptor blockers, determining unchanged whole-day urinary sodium excretion and diminished whole-day urinary potassium excretion [68].

The extent of derangement in renal function may be reliably appraised by means of evaluation of excretory function together with proteinuria, providing independent relationships of estimated glomerular filtration rate and proteinuria with the circadian variation and the mean level of blood pressure. The mean level of systolic and diastolic blood pressure increases with increasing severity of proteinuria as well as with increasing impairment in glomerular filtration rate, with a graded relationship of proteinuria and glomerular filtration rate with the mean level of blood pressure and a non-graded relationship with circadian variation [69]. In children affected by chronic glomerulopathy with reduced creatinine clearance the 24-h urine volume output, urine creatinine and urine sodium excretion were comparable to those observed in children affected by chronic glomerulopathy with normal creatinine clearance, but they showed greater proteinuria, arterial hypertension and nocturnal polyuria. Besides, the nocturnal decline in creatinine clearance, urine volume output, urine sodium excretion and proteinuria were significantly attenuated and the nighttime mean arterial pressure, as well as the night/day ratios of mean arterial pressure, urine volume output, urine sodium excretion and proteinuria showed negative associations with creatinine clearance [70].

The circadian clock circuitry in kidney disease

Severe alterations of sleep quality, timing and duration are characteristic of chronic kidney disease. Studies performed in an animal model of chronic kidney disease represented by the 5/6th nephrectomized Sprague–Dawley rat have put in evidence sleep disturbances, with the increase of both slow wave sleep and rapid-eye movement sleep in the middle part of the dark period, and the mRNA expression of clock genes *PER1* and *PER2* was up-regulated in the hypothalamus [71]. Circadian sleep–wake cycle disturbances frequently lessen the quality of life in individuals with end-stage renal disease, and sleep disorders, caused both by the pathology of the renal disease and by the dialysis treatment itself, are much more prevalent in the dialysis population than in the general population, impinging greatly on the vitality and general health of these patients. The effect of dialysis, medications and biochemical parameters may represent external and internal influences on sleep–wake rhythmicity in patients with end-stage renal disease [72]. Comparative data on sleep–wake rhythms in different dialysis groups have been reported by a study that examined sleep–wake parameters measured with actigraphy and sleep questionnaires as well as melatonin

rhythms in automated peritoneal dialysis, conventional daytime hemodialysis and nocturnal hemodialysis patients. Conventional daytime dialysis patients had the worst sleep, a normal nocturnal melatonin rise was found in nocturnal hemodialysis patients, whereas this rise was absent in daytime hemodialysis and automated peritoneal dialysis patients [72]. Another study reported improvements in polysomnography, sleep quality/efficiency and deep sleep, rapid-eye-movement sleep, awake time, and oxygen saturation and partial rescue of nocturnal melatonin surge after 6 months of in-center nocturnal hemodialysis therapy [73]. The evidence draws attention to the urgent need for intervention strategies to effectively strengthen the synchronization of the circadian sleep–wake rhythm, such as nocturnal hemodialysis, dialyzate temperature, use of bright light and exercise during dialysis treatment, exogenous erythropoietin and exogenous melatonin [74, 75]. Chronic kidney disease by itself alters the endocrine secretory output of the circadian timing system. In this regard, the amplitude of melatonin rhythm decreases with advancing renal dysfunction [76] and the administration of exogenous melatonin (3 mg at 22.00 h every night) improves subjective and objective sleep parameters, rescuing nocturnal melatonin rhythm in hemodialysis patients [74]. On the other hand, renal function does not seem to associate with cortisol rhythm parameters, and no association could be detected between the phases of the rhythms of melatonin and cortisol [77]. Substantial disagreement originated from the evaluation of the hypothalamic–pituitary–adrenal axis function in patients with chronic kidney disease, and in this patient population the diagnosis of anomalous glucocorticoid metabolism can be not simple. The excretion of cortisol and its water soluble metabolites depends on normal kidney function, and in advanced renal failure there is lengthening of cortisol serum half-life [78], cortisol binding to corticosteroid-binding globulin remains normal, while binding to albumin is decreased, and compounds comprising cortisol metabolites accumulate, interfering with cortisol measurement, so that methodological problems produce conflicting results, and both normal and elevated levels of serum cortisol are described [79, 80]. The features of endogenous hypercortisolism may be present in patients with end-stage renal disease, and when evaluations of cortisol and ACTH were performed in plasma and salivary samples drawn frequently over 24 h in subjects on daytime chronic hemodialysis, higher nadir in plasma and salivary cortisol and plasma ACTH secretion was evidenced, so that end-stage renal disease patients had increased late-night plasma and salivary cortisol and plasma ACTH levels when compared with controls [81].

The functioning of the clock gene machinery has been evaluated in patients affected by kidney cancer, and the expression of a number of clock genes was altered [82]. Down-regulation was evidenced in tumor tissue when compared with matched non-tumorous tissue for *PER2*, involved in susceptibility to DNA damage-induced carcinogensis, and for *TIMELESS* and *TIPIN*, which in conjunction with *PER2* interact with cell cycle checkpoints and take part in the response to DNA damage. On the contrary, up-regulation was evidenced for *ARNTL2* and the downstream target gene *SERPINE1*,

encoding the (PAI-1), seemingly implicated in hypercoagulability state and increased frequency of thrombotic events, such as mono or bilateral renal vein thrombosis, which influence overall survival in kidney cancer patients [82]. The alteration of the clock gene machinery evidenced in kidney cancer and the control of cellular proliferation and drug metabolism over the 24 h by circadian clocks open the way to therapeutic approaches that take into account the temporal dimension of drug administration, i.e. chronotherapy, based on timing models to optimize the scheduling of anti-cancer drugs, with the aim to deal with the rhythm of both the anti-cancer action of drugs, and that of drug-related side effects on normal cells [83].

CONCLUSION

Kidney functions, such as hydro-electrolytic and acid-base balance regulation, small solutes reabsorption and hormone production, are characterized by diurnal changes and contribute to circadian variability of blood pressure and to daily oscillation in body homeostasis. The circadian clock circuitry drives the rhythmicity of renal physiology controlling nychthemeral changes of sodium sensitivity, vascular tone, autonomic function and neurotransmitter release from sympathetic innervations, as well as behavioral cycles of rest/activity and sleep–wake. The mismatch between environmental–social cues and physiological–behavioral patterns, triggers physiopathological mechanisms involved in renal pathology. During the last years, numerous advances have provided a better understanding of the role of the molecular clockwork on renal function, especially in the control of salt and blood pressure, and of biological clock derangements in renal disease. Other fields of renal physiology, known to harbor circadian cyclicity, as well as renal pathology, related to desynchronization of periodic functions, need to be explored.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format.

REFERENCES

1. Mazzoccoli G. The timing clockwork of life. J Biol Regul Homeost Agents 2011; 25: 137–143
2. Bass J. Circadian topology of metabolism. Nature 2012; 491: 348–356
3. Mazzoccoli G, Pazienza V, Vinciguerra M. Clock genes and clock-controlled genes in the regulation of metabolic rhythms. Chronobiol Int 2012; 29: 227–251
4. Vollmers C, Gill S, Di Tacchio L et al. Time of feeding and the intrinsic circadian clock drive rhythms in hepatic gene expression. Proc Natl Acad Sci USA 2009; 106: 21453–21458
5. Hsieh MC, Yang SC, Tseng HL et al. Abnormal expressions of circadian-clock and circadian clock-controlled genes in the livers and kidneys of long-term, high-fat-diet-treated mice. Int J Obes (Lond) 2010; 34: 227–239
6. Agarwal R. Regulation of circadian blood pressure: from mice to astronauts. Curr Opin Nephrol Hypertens 2010; 19: 51–58
7. Firsov D, Tokonami N, Bonny O. Role of the renal circadian timing system in maintaining water and electrolytes homeostasis. Mol Cell Endocrinol 2012; 349: 51–55
8. Buxton OM, Cain SW, O'Connor SP et al. Adverse metabolic consequences in humans of prolonged sleep restriction combined with circadian disruption. Sci Transl Med 2012; 4: 129ra143
9. Liu S, Cai Y, Sothern RB et al. Chronobiological analysis of circadian patterns in transcription of seven key clock genes in six peripheral tissues in mice. Chronobiol Int 2007; 24: 793–820
10. Duong HA, Robles MS, Knutti D et al. A molecular mechanism for circadian clock negative feedback. Science 2011; 332: 1436–1439
11. Cho H, Zhao X, Hatori M et al. Regulation of circadian behaviour and metabolism by REV-ERB-α and REV-ERB-β. Nature 2012; 485: 123–127
12. Lee J, Lee Y, Lee MJ et al. Dual modification of BMAL1 by SUMO2/3 and ubiquitin promotes circadian activation of the CLOCK/BMAL1 complex. Mol Cell Biol 2008; 28: 6056–6065
13. Agostino PV, Harrington ME, Ralph MR et al. Casein kinase-1-epsilon (CK1epsilon) and circadian photic responses in hamsters. Chronobiol Int 2009; 26: 126–133
14. Sahar S, Zocchi L, Kinoshita C et al. Regulation of BMAL1 protein stability and circadian function by GSK3beta-mediated phosphorylation. PLoS One 2010; 5: e8561
15. Nakahata Y, Kaluzova M, Grimaldi B et al. The NAD+-dependent deacetylase SIRT1 modulates CLOCK-mediated chromatin remodeling and circadian control. Cell 2008; 134: 329–340
16. Feng D, Liu T, Sun Z et al. A circadian rhythm orchestrated by histone deacetylase 3 controls hepatic lipid metabolism. Science 2011; 331: 1315–1319
17. Smith KD, Fu MA, Brown EJ. Tim-Tipin dysfunction creates an indispensible reliance on the ATR-Chk1 pathway for continued DNA synthesis. J Cell Biol 2009; 187: 15–23
18. Nakashima A, Kawamoto T, Honda KK et al. DEC1 modulates the circadian phase of clock gene expression. Mol Cell Biol 2008; 28: 4080–4092
19. Gachon F, Olela FF, Schaad O et al. The circadian PAR-domain basic leucine zipper transcription factors DBP, TEF, and HLF modulate basal and inducible xenobiotic detoxification. Cell Metab 2006; 4: 25–36

20. Bozek K, Relógio A, Kielbasa SM et al. Regulation of clock-controlled genes in mammals. PLoS One 2009; 4: e4882

21. Lowrey PL, Takahashi JS. Genetics of circadian rhythms in mammalian model organisms. Adv Genet 2011; 74: 175–230

22. Kalsbeek A, Palm IF, La Fleur SE et al. SCN outputs and the hypothalamic balance of life. J Biol Rhythms 2006; 21: 458–469

23. Challet E. Entrainment of the suprachiasmatic clockwork in diurnal and nocturnal mammals. Endocrinology 2007; 148: 5648–5655

24. Schwimmer H, Mursu N, Haim A. Effects of light and melatonin treatment on body temperature and melatonin secretion daily rhythms in a diurnal rodent, the fat sand rat. Chronobiol Int 2010; 27: 1401–1419

25. Lardone PJ, Guerrero JM, Fernández-Santos JM et al. Melatonin synthesized by T lymphocytes as a ligand of the retinoic acid-related orphan receptor. J Pineal Res 2011; 51: 454–462

26. Yamamoto T, Nakahata Y, Tanaka M et al. Acute physical stress elevates mouse period1 mRNA expression in mouse peripheral tissues via a glucocorticoid- responsive element. J Biol Chem 2005; 280: 42036–42043

27. Bonny O, Firsov D. Circadian regulation of renal function and potential role in hypertension. Curr Opin Nephrol Hypert 2013; 22: 439–444

28. Dibner C, Schibler U, Albrecht U. The mammalian circadian timing system: organization and coordination of central and peripheral clocks. Annu Rev Physiol 2010; 72: 517–549

29. Mazzoccoli G, Sothern RB, Greco A et al. Time-related dynamics of variation in core clock gene expression levels in tissues relevant to the immune system. Int J Immunopathol Pharmacol 2011; 24: 869–879

30. Mazzoccoli G, Cai Y, Liu S et al. REV-ERBalpha and the clock gene machinery in mouse peripheral tissues: a possible role as a synchronizing hinge. J Biol Regul Homeost Agent 2012; 26: 265–276

31. Wu T, Ni Y, Dong Y et al. Regulation of circadian gene expression in the kidney by light and food cues in rats. Am J Physiol Regul Integr Comp Physiol 2010; 298: R635–R641

32. Wu T, Fu O, Yao L, Sun L, Zhuge F, Fu Z. Differential responses of peripheral circadian clocks to a short-term feeding stimulus. Mol Biol Rep 2012; 39: 9783–9789

33. Zuber AM, Centeno G, Pradervand S et al. Molecular clock is involved in predictive circadian adjustment of renal function. Proc Natl Acad Sci USA 2009; 106: 16523–16528

34. Moore-Ede MC. Physiology of the circadian timing system: predictive versus reactive homeostasis. Am J Physiol 1986; 250: R737–R752

35. Saifur Rohman M, Emoto N, Nonaka H et al. Circadian clock genes directly regulate expression of the Na(+)/H(+) exchanger NHE3 in the kidney. Kidney Int 2005; 67: 1410–1419

36. Nishinaga H, Komatsu R, Doi M et al. Circadian expression of the Na+/H+ exchanger NHE3 in the mouse renal medulla. Biomed Res 2009; 30: 87–93

37. Gumz ML, Stow LR, Lynch IJ et al. The circadian clock protein Period 1 regulates expression of the renal epithelial sodium channel in mice. J Clin Invest 2009; 119: 2423–2434

38. Gumz ML, Cheng KY, Lynch IJ et al. Regulation of alphaENaC expression by the circadian clock protein Period 1 in mpkCCD (c14) cells. Biochim Biophys Acta 2010; 1799: 622–629

39. Richards J, Greenlee MM, Jeffers LA et al. Inhibition of alphaE-NaC expression and ENaC activity following blockade of the circadian clock-regulatory kinases CKIdelta/{varepsilon}. Am J Physiol Renal Physiol 2012; 303: F918–F927

40. Stow LR, Richards J, Cheng KY et al. The circadian protein period 1 contributes to blood pressure control and coordinately regulates renal sodium transport genes. Hypertension 2012; 59: 1151–1156

41. Salhi A, Centeno G, Firsov D et al. Circadian expression of H,K-ATPase type 2 contributes to the stability of plasma K(+) levels. FASEB J 2012; 26: 2859–2867

42. Krid H, Dorison A, Salhi A et al. Expression profile of nuclear receptors along male mouse nephron segments reveals a link between ERRbeta and thick ascending limb function. PLoS One 2012; 7: e34223

43. Balsalobre A, Brown SA, Marcacci L et al. Resetting of circadian time in peripheral tissues by glucocorticoid signaling. Science 2000; 289: 2344–2347

44. Lamia KA, Papp SJ, Yu RT et al. Cryptochromes mediate rhythmic repression of the glucocorticoid receptor. Nature 2011; 480: 552–556

45. Alvarez JD, Hansen A, Ord T et al. The circadian clock protein BMAL1 is necessary for fertility and proper testosterone production in mice. J Biol Rhythms 2008; 23: 26–36

46. Lefta M, Campbell KS, Feng HZ et al. Development of dilated cardiomyopathy in Bmal1-deficient mice. Am J Physiol Heart Circ Physiol 2012; 303: H475–H485

47. Wang Q, Maillard M, Schibler U et al. Cardiac hypertrophy, low blood pressure, and low aldosterone levels in mice devoid of the three circadian PAR bZip transcription factors DBP, HLF, and TEF. Am J Physiol Regul Integr Comp Physiol 2010; 299: R1013–R1019

48. Turek FW, Joshu C, Kohsaka A et al. Obesity and metabolic syndrome in circadian Clock mutant mice. Science 2005; 308: 1043–1045

49. Doi M, Takahashi Y, Komatsu R et al. Salt-sensitive hypertension in circadian clock-deficient Cry-null mice involves dysregulated adrenal Hsd3b6. Nat Med 2010; 16: 67–74

50. Vukolic A, Antic V, Van Vliet BN et al. Role of mutation of the circadian clock gene Per2 in cardiovascular circadian rhythms. Am J Physiol Regul Integr Comp Physiol 2010; 298: R627–R634

51. Nikolaeva S, Pradervand S, Centeno G et al. The circadian clock modulates renal sodium handling. J Am Soc Nephrol 2012; 23: 1019–1026.

52. Stow LR, Gumz ML. The circadian clock in the kidney. J Am Soc Nephrol 2011; 22: 598–604

53. Bugaj V, Pochynyuk O, Mironova E et al. Regulation of the epithelial Na+ channel by endothelin-1 in rat collecting duct. Am J Physiol Renal Physiol 2008; 295: F1063–F1070

54. Ahn D, Ge Y, Stricklett PK et al. Collecting duct-specific knockout of endothelin-1 causes hypertension and sodium retention. J Clin Invest 2004; 114: 504–511

55. Martino TA, Oudit GY, Herzenberg AM et al. Circadian rhythm disorganization produces profound cardiovascular and renal disease in hamsters. Am J Physiol Regul Integr Comp Physiol 2008; 294: R1675–R1683

56. Wu T, Ni Y, Zhuge F et al. Significant dissociation of expression patterns of the basic helix-loop-helix transcription factors Dec1 and Dec2 in rat kidney. J Exp Biol 2011; 214: 1257–1263

O. Bonny et al.

57. Oike H, Nagai K, Fukushima T *et al*. High-salt diet advances molecular circadian rhythms in mouse peripheral tissues. Biochem Biophys Res Commun 2010; 402: 7–13

58. Negoro H, Kanematsu A, Yoshimura K *et al*. Chronobiology of micturition: putative role of the circadian clock. J Urol 2013. pii: S0022-5347(13)00293-0. doi:10.1016/j.juro.2013.02.024 [Epub ahead of print]

59. Mazzoccoli G, Francavilla M, Giuliani F *et al*. Clock gene expression in mouse kidney and testis: analysis of periodical and dynamical patterns. J Biol Regul Homeost Agents 2012; 26: 303–311

60. Rudic RD, Fulton DJ. Pressed for time: the circadian clock and hypertension. Appl Physiol 2009; 107: 1328–1338

61. Susa K, Sohara E, Isobe K *et al*. WNK-OSR1/SPAK-NCC signal cascade has circadian rhythm dependent on aldosterone. Biochem Biophys Res Commun 2012; 427: 743–747

62. Pons M, Schnecko A, Witte K *et al*. Circadian rhythms in renal function in hypertensive TGR(mRen-2)27 rats and their normotensive controls. Am J Physiol 1996; 271: R1002–R1008

63. Herichová I, Mravec B, Stebelová K *et al*. Rhythmic clock gene expression in heart, kidney and some brain nuclei involved in blood pressure control in hypertensive TGR(mREN-2)27 rats. Mol Cell Biochem 2007; 296: 25–34

64. Hermida RC, Ayala DE, Portaluppi F. Circadian variation of blood pressure: the basis for the chronotherapy of hypertension. Adv Drug Deliv Rev 2007; 59: 904–922

65. Hermida RC, Ayala DE, Smolensky MH *et al*. Chronotherapy improves blood pressure control and reduces vascular risk in CKD. Nat Rev Nephrol 2013; 9: 358–368

66. Kimura G, Dohi Y, Fukuda M. Salt sensitivity and circadian rhythm of blood pressure: the keys to connect CKD with cardiovascular events. Hypertens Res 2010; 33: 515–520

67. Miura T, Fukuda M, Naito T *et al*. Circadian rhythm of urinary potassium excretion in patients with CKD. Clin Nephrol 2012; 78: 169–173

68. Ogiyama Y, Miura T, Watanabe S *et al*. Circadian rhythm of urinary potassium excretion during treatment with an angiotensin receptor blocker. J Renin Angiotensin Aldosterone Syst 2013 [Epub ahead of print]

69. Agarwal R, Light RP. GFR, proteinuria and circadian blood pressure. Nephrol Dial Transplant 2009; 24: 2400–2406

70. Peco-Antić A, Marinković J, Kruscić D *et al*. Circadian rhythms of diuresis, proteinuria and natriuresis in children with chronic glomerular disease. Pediatr Nephrol 2009; 24: 1165–1172

71. Hsu CY, Chang FC, Ng HY *et al*. Disrupted circadian rhythm in rats with nephrectomy-induced chronic kidney disease. Life Sci 2012; 91: 127–131

72. Koch BC, Nagtegaal JE, Hagen EC *et al*. Different melatonin rhythms and sleep–wake rhythms in patients on peritoneal dialysis, daytime hemodialysis and nocturnal hemodialysis. Sleep Med 2010; 11: 242–246

73. Koch BC, Hagen EC, Nagtegaal JE *et al*. Effects of nocturnal hemodialysis on melatonin rhythm and sleep–wake behavior: an uncontrolled trial. Am J Kidney Dis 2009; 53: 658–664

74. Koch BC, Nagtegaal JE, Hagen EC *et al*. The effects of melatonin on sleep–wake rhythm of daytime haemodialysis patients: a randomized, placebo-controlled, cross-over study (EMSCAP study). Br J Clin Pharmacol 2009; 67: 68–75

75. Aperis G, Prakash P, Paliouras C *et al*. The role of melatonin in patients with chronic kidney disease undergoing haemodialysis. J Ren Care 2012; 38: 86–92

76. Koch BC, van der Putten K, Van Someren EJ *et al*. Impairment of endogenous melatonin rhythm is related to the degree of chronic kidney disease (CREAM study). Nephrol Dial Transplant 2010; 25: 513–519

77. Koch BC, Nagtegaal JE, Kerkhof GA *et al*. Circadian sleep–wake rhythm disturbances in end-stage renal disease. Nat Rev Nephrol 2009; 5: 407–416

78. Bacon GE, Kenny FM, Murdaugh HV *et al*. Prolonged serum half-life of cortisol in renal failure. Johns Hopkins Med J 1973; 132: 127

79. Rosman PM, Benn R, Kay M *et al*. Cortisol binding in uremic plasma. II. Decreased cortisol binding to albumin. Nephron 1984; 37: 229

80. Nolan GE, Smith JB, Chavre VJ *et al*. Spurious overestimation of plasma cortisol in patients with chronic renal failure. J Clin Endocrinol Metab 1981; 52: 1242

81. Raff H, Trivedi H. Circadian rhythm of salivary cortisol, plasma cortisol, and plasma ACTH in end-stage renal disease. Endocrine Connections 2013; 2: 23–31

82. Mazzoccoli G, Piepoli A, Carella M *et al*. Altered expression of the clock gene machinery in kidney cancer patients. Biomed Pharmacother 2012; 66: 175–179

83. Levi F, Schibler U. Circadian rhythms: mechanisms and therapeutic implications. Annu Rev Pharmacol Toxicol 2007; 47: 593–628

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