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The Circadian Clock in the Kidney

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Abstract

Circadian variations in renal function were first described in the 19th century, and GFR, renal blood flow, urine production, and electrolyte excretion exhibit daily oscillations. These clinical observations are well established, but the underlying mechanisms that govern circadian fluctuations in kidney are not fully understood. Here we provide a brief overview of the machinery governing the circadian clock and examine the clinical and molecular evidence supporting a critical role for circadian rhythm in the kidney. There is a connection between BP oscillation and renal disease that supports the use of chronotherapy in the treatment of hypertension or correction of nondipping BP. Such studies support a developing model of clock controlled sodium and water transport in renal epithelial cells. Recent advances in identifying novel clock-controlled genes using rodent and cellular models also shed light on the molecular mechanisms by which the circadian clock controls renal function; however, the field is new and much more work remains.

Most physiologic processes, including sleep-wake patterns, heartbeat, and systemic arterial BP, exhibit a circadian pattern of variation. The word circadian is derived from the Latin words *circa* and *dies*, meaning about a day. The term circadian is used here to denote biologic processes that occur with a daily, or approximately a 24-hour rhythm. A more stringent definition of circadian is used in studies of biologic rhythms to describe oscillations that occur under constant conditions; a process is considered truly circadian only if the oscillation is maintained in the absence of external zeitgeibers, or time cues such as light/dark cycles. It has been over a century since Vogel first reported daily fluctuations in urine volume.[1] Healthy individuals excrete more electrolytes and produce more urine during the day than at night, and there are diurnal rhythms for urinary sodium, potassium, and chloride excretion.[2] Disruption of these patterns is often associated with hypertension and cardiovascular disease.[3,4]

The master pacemaker of the circadian clock is located in the suprachiasmatic nucleus (SCN) of the brain. This central clock is entrained by light signals transmitted from the retina through the retinohypothalamic tract. A core group of clock genes functions in a series of transcription-based feedback loops (Figure 1). Transcription factors, Bmal1 and Clock, drive the transcription of the Period (*Per1, 2*, and *3*) and Cryptochrome (*Cry1* and *2*) genes

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and nuclear receptor genes, *ROR* and *Rev-erbα*. The Bmal1/Clock heterodimer regulates gene expression by binding E-box response elements (CANNTG) in the promoter region of target genes. Period and Cryptochrome inhibit Bmal1 and Clock action, thereby repressing their own transcription, whereas ROR and Rev-erbα mediate opposing action on *Bmal1* expression.[5,6] Post-translational modification controls stability and nuclear entry of clock proteins, contributes to the precise timing of the clock mechanism, and is thought to allow crosstalk between physiology and the clock.[5,7] In addition to regulating each other to maintain oscillation, the core clock proteins regulate genes that mediate physiologic functions governed by circadian rhythm. These clock-controlled output genes constitute up to 15% of expressed transcripts in some tissues.[8]

The core clock machinery has been identified in nearly every peripheral tissue. The master clock in the SCN synchronizes the functions of these peripheral clocks through neuronal and humoral signaling.[9] As well, body temperature, rest-activity cycles, and feeding cycles contribute to entrainment of the peripheral clocks. Although the relationship between the central and peripheral clocks has been described as co-dependent, the peripheral clocks do not respond identically to cues from the SCN.[10–12] Thus, study of the clock in individual tissues is necessary. The role of circadian rhythms has recently been reviewed for the cardiovascular system,[13] the vasculature,[14,15] metabolic syndrome,[16] and the gastrointestinal system.[17] Here we examine the clinical and molecular evidence supporting a critical role for the clock in the control of renal function.

ROLE OF THE CIRCADIAN CLOCK IN THE KIDNEY: CLINICAL EVIDENCE

Nondipping BP and the Kidney

Cardiovascular events such as stroke and myocardial infarction are known to peak with the morning surge in BP and heart rate. BP increases in the early morning, followed by a plateau during the day, and then dips during sleep.[18] Patients who do not exhibit a 10 to 20% decrease in nighttime *versus* daytime BP are designated “nondippers” and are at increased risk of cardiac death.[19] Nondippers exhibit increased left ventricular hypertrophy, carotid artery wall thickness and atherosclerotic plaques, microalbuminuria, cerebrovascular disease, congestive heart failure, vascular dementia, stroke, and myocardial infarction.[20] Importantly, nondipping may predict renal damage.[21]

Several reports link aldosterone signaling to the disruption of circadian BP patterns, suggesting a role for renal function in maintaining normal circadian changes in BP. Patients suffering from aldosteronism exhibit the nondipper pattern,[22,23] and treatment with the angiotension II receptor blocker, irbesartan corrects the nondipper pattern in salt-sensitive hypertension.[24] The diuretic hydrocholorothiazide restores an appropriate decrease in nocturnal BP in non-dipping patients but had no effect in dippers.[25] Furthermore, dietary sodium restriction re-establishes the nocturnal dipping pattern.[26] Nondipping associates with an increased risk of nephropathy[27] and chronic kidney disease.[28] Importantly, renal transplantation can rescue the nondipping phenotype,[29] although a lack of nocturnal variation can portend poor allograft survival.[30] Collectively, these findings suggest a direct link between abnormal circadian patterns in BP and inappropriate sodium transport in the kidney.

Salt handling by the kidney has long been recognized as a critical determinant of BP, and hypertension is rarely observed in the absence of renal dysfunction.[31] A decline in renal function directly correlates with a nondipping phenotype. A well-controlled study showed that creatinine clearance declines more rapidly in nondippers compared with dippers, and urinary protein excretion is greater in the nondippers compared with dippers.[32] The nondipping phenotype also associates with a faster decline in renal function, and the authors suggested that regulation of nocturnal BP should be an additional goal of anti-hypertensive treatment. Similarly, Agarwal and Light[33] determined that a nondipping status was a significant predictor of chronic kidney disease and proteinuria and inferred that correction of dipper status could be an effective therapy for kidney disease. Taken together, these studies showed the important relationship between renal physiology and the circadian pattern of BP.

Chronotherapy in the Treatment of Hypertension

Increasing evidence supports a critical role for the circadian clock in human health. Chronotherapy, the scheduled administration of pharmaceutical agents with respect to an individual's circadian rhythms, may increase the effectiveness and decrease the side effects of pharmacologic agents.[34,35] Chronotherapy has been investigated in the treatment of many nonrenal diseases[36–40] and has been proposed for treatment of diabetes,[41] cardiac arrhythmias,[42] and ischemic heart disease.[43]

The potential benefits of chronotherapy in the treatment of hypertension include control of BP and normalization of the dipping pattern.[44] Cross-sectional and longitudinal studies consistently show that nondipping is a preclinical marker for cardiovascular and renal disease and can be used to predict cardiovascular events.[45] Indeed, accruing evidence suggests that nighttime BP is a more important indicator of cardiovascular health than daytime values.[46,47] One example comes from a convincing study in which previously untreated hypertensive patients were randomized into groups receiving a single daily dose of ramipril either in the morning or at bedtime.[48] BP during sleep was significantly reduced in bedtime-dosed patients compared with morning-dosed patients. Notably, nighttime dosing also increases the effectiveness of ramipril as BP reduction lasted 24 hours after bedtime dosing compared with 16 hours after morning dosing.

The effect of nighttime administration of anti-hypertensive drugs in nondipping patients has been tested in geographically distinct populations.[49,50,51] Anti-hypertensive therapy delivered as an evening dose is highly effective at correcting the nondipping phenotype. Bedtime administration of valsartan, doxazosin (extended release), torasemid, or long-acting nifedipine improves efficacy and reduces side effects of anti-hypertensive treatment.[52] These studies highlight the importance of evaluating the 24-hour BP profile as opposed to single, daytime office measurements. Although these results are promising, larger, more comprehensive trials are needed. A reduction in all-cause mortality would be a convincing outcome. A long-term study following thousands of subjects, the recently completed Monitorización Ambulatoria de la Presión Arterial y Eventos Cardiovasculares—Ambulatory Blood Pressure Monitoring and Cardiovascular Events (MAPEC) trial, was designed to determine whether restoring the dipper pattern using chronotherapy decreases the risk of cardiovascular disease.[53] Providing evidence for the use of chronotherapy in

hypertension, the MAPEC results demonstrate that bedtime drug administration, compared to conventional upon-awakening therapy, was more effective at controlling BP and decreasing non-dipping, and resulted in significant reduction of cardiovascular morbidity and mortality.[54]

Circadian Disturbances in Dialysis Patients

Melatonin is an important regulator of the circadian sleep-wake cycle. In healthy individuals, the pineal gland produces melatonin at night; light exposure suppresses melatonin production. The expected nighttime peak in melatonin levels is lost in patients undergoing hemodialysis, and decreased melatonin levels associate with more severe sleep disturbances in these patients. Interestingly, patients receiving nocturnal dialysis experienced the normal nighttime peak in melatonin and reported better sleep quality compared with daytime dialysis patients.[55] A recent study in patients with chonic kidney disease (CKD) found that melatonin amplitude decreases with advancing renal disease, emphasizing the need for further investigation into circadian mechanisms in CKD patients.[55]

Patients undergoing dialysis treatment are more prone to sleep disturbances compared with the general population, resulting in a negative impact on overall health and quality of life. Non-dipping CKD patients seem to have poor sleep quality.[56] Circadian sleep-wake disturbances are common in ESRD patients.[57] Renal disease and dialysis treatment may contribute to the etiology of sleep disturbances in dialysis patients independently of each other. Up to 80% of ESRD patients have reported subjective sleep problems. Daytime sleepiness is increased by dialysis, and this effect is the result of several factors, including elevated body temperature during treatment and the physical and emotional stress caused by the procedure. Likewise, sleep disturbances are a common side effect of medications prescribed to ESRD patients, including β-blockers and benzodiazepines. Several treatments aimed at resynchronizing the sleep-wake rhythm in hemodialysis patients result in some level of sleep improvement.[57] These include a switch to nocturnal hemodialysis, lowering the temperature of the dialyzate, exercise during dialysis, administration of melatonin, or exogenous erythropoietin treatment. Bright light therapy might also benefit hemodialysis patients with circadian sleep disruption.[57]

Circadian Influence on Renal Function

In addition to a role for the kidney in maintaining proper BP rhythms, renal function oscillates in a circadian manner with daily fluctuations in renal blood flow and GFR[58] and the excretion of electrolytes such as sodium and potassium.[59] Likewise, urinary excretion of phosphate, magnesium, and acid oscillates with a circadian pattern.[60,61] Although these clinical observations have been well established, the underlying molecular mechanisms are unclear.

MOLECULAR EVIDENCE FOR THE ROLE OF A CIRCADIAN CLOCK IN THE KIDNEY

Transcriptional Regulation of Renal Gene Expression by the Circadian Clock

A growing number of genes are regulated by transcriptional mechanisms of the circadian clock. Many clock-controlled genes have been identified in the kidney through either gene expression profiling or candidate gene approaches (Table 1). The term “clock-controlled gene” is used here to describe genes that exhibit rhythmic expression. Most of the genes listed in Table 1 have only recently been linked to the circadian clock, and it remains to be determined whether circadian clock proteins interact with E-box elements in the promoters of these genes.

These genes encode products that range from transcription regulators[62] to cell junction proteins.[63,64] Although the implications of clock-mediated regulation of these genes are not yet clear, it is interesting that the function of the transcription repressor, Kid-1 (kidney, ischemia, developmentally-regulated gene 1),[65] is linked to regulation of extracellular signal-regulated kinases,[66] providing an intriguing link between a clock-controlled gene and signal transduction in the kidney. Furthermore, the rhythmic expression of E-cadherin and claudin-4 seemed to parallel the circadian changes observed in sodium excretion.[63]

The circadian clock gene *Period 1* (*Per1*) was identified as a novel aldosterone target in a murine inner medullary collecting duct cell line and was the most highly induced transcript in the entire study.[67] Per1 contributes to the basal and aldosterone-dependent transcription of *Scnn1a*, which encodes the rate-limiting subunit of the epithelial sodium channel.[68] *Scnn1a* expression is reduced in the renal medulla of *Per1* null mice. *Per1*-null mice excrete more urinary sodium than wild-type mice, although the mechanism of this effect is unknown. The apparent circadian expression of *Scnn1a* is also altered in mice lacking all three *Period* genes compared with wild-type mice. Given the critical role of the rate-limiting subunit of the epithelial sodium channel in sodium transport and BP control, these results implicate the clock in the mechanism underlying the known daily fluctuations in sodium excretion and BP.

Many renal transport genes have been identified as clock-controlled genes (Table 2). NHE3 was the first transporter in the kidney to be identified as a target of the clock transcription mechanism.[69] mRNA encoding *NHE3* is expressed in a circadian manner in wild-type rodents, but rhythmic expression is blunted in *Cry1/Cry2*-null mice. A specific E-box response element is required for Bmal1/Clock-mediated transactivation of *NHE3* promoter activity. Consistent with this observation is a recent report describing the presence of an E-box in the *Scnn1a* promoter that is bound by Clock and Per1.[70] Together these studies provide direct molecular evidence for regulation of transport gene expression by the circadian clock.

In the first study of its kind, Zuber *et al.*[64] used microarray analysis to profile the expression of circadian genes in microdissected distal nephron and collecting duct segments over a 24-hour period. Hundreds of putative clock-controlled genes were identified. Circadian expression of selected genes was confirmed in independent samples, and these genes are included in Tables 1 and 2. These novel clock targets encode moieties ranging from known

regulators of sodium transport to critical regulators of water balance. Many of the genes listed in Table 2 are expressed in principal cells of the cortical collecting duct, and the products of these genes contribute to sodium and water transport (Figure 2). Further study will likely identify additional clock-controlled genes, providing additional insight into the mechanism by which the circadian clock regulates water and electrolyte transport in the kidney.

Rodent Models of Circadian Disorganization

Casein kinase Iε-mediated phosphorylation controls stability of the Period proteins. *tau* mutant hamsters have a gain-of-function mutation in casein kinase Iε and display a shortened circadian period. Heterozygous *tau* mutants display a severe cardiorenal phenotype characterized by cardiomyopathy, hypertrophy, cardiac fibrosis, and early death[71]; renal dysfunction is manifested as proteinuria, tubular dilation, glomerular ischemia, and cellular apoptosis. SCN ablation in young adult *tau* mutant hamsters rescues the cardiac hypertrophy phenotype. Moreover, the cardiorenal phenotype is reversed and longevity is restored when the *tau* mutants are maintained on a shorter 22-hour light/dark cycle.

The mouse *renin* transgenic rat [TGR(m-REN2)27] is also a well-characterized model of hypertension. These animals have an inverted circadian BP profile and consequent end-organ damage.[72] *TGR* rats exhibit a profound circadian phenotype in which the normal circadian pattern of core clock gene expression, signal transduction pathways, and sympathetic nervous system activity is altered severely.[73] Consistent with human studies discussed above, the renin-angiotensin-aldosterone system contributes to maintenance of circadian rhythms in rodents.

Reports of BP phenotypes in rodents with circadian clock disruption suggest that the clock is critical for cardiovascular function. Whereas *Clock*-null mice maintain a normal 24-hour rhythm of BP, the average mean arterial pressure and mean systolic BP were significantly lower in these mice compared with wild type.[64] These mice display altered rhythms in urinary sodium excretion and a mild diabetes insipidus.

When maintained on a standard 12-hour light/dark cycle, *Per2* mutant mice exhibit decreased 24-hour diastolic BP, increased heart rate, and a decreased difference between day and night BP.[71] Under constant darkness, wild-type mice maintained normal 24-hour rhythms in BP, activity, and heart rate, but *Per2* mutant mice experienced a shortened circadian period.

Salt-sensitive hypertension was observed in *Cry1/Cry2* knockout mice.[75] Elevated plasma aldosterone levels were observed in these mice, leading the investigators to perform microarray analysis of adrenal glands from *Cry1/Cry2*-null mice compared with wild type. *Hsd3b6*, a dehydrogenase-isomerase in the aldosterone synthesis pathway, was identified as a highly overexpressed gene in null mice. Increased activity of this enzyme was recorded in *Cry1/Cry2* knockout mice and was linked to the observed salt-sensitive hypertension. Importantly, this study identified a putative target for interventional therapy in hypertensive patients. Given that the HSD3B6 enzyme catalyzes a relatively early reaction in the steroid

hormone synthesis pathway (pregnenolone to progesterone), it will be interesting to see what other steroid hormonesare elevated in these mice and how this defect influences the long-term health of these circadian mutant animals.

THE FUTURE

A critical issue is what proportion of circadian fluctuations in renal function is caused by the influence of the central clock in the SCN *versus* an intrinsic clock in the kidney alone. Renal tissue explants from *Per2/luciferase* transgenic mice oscillate in culture, and this effect is maintained after SCN ablation.[10] Uncoupling of the peripheral clocks from the central clock by food restriction is another way to address this issue. Reversal of the light/dark cycle and the feeding schedule causes a phase shift in the expression of clock genes in rat kidney.[76] *Per1* and *Clock* appeared to be the most sensitive to these changes. An important tool in determining the role of the clock in individual tissues is the generation of tissue specific null mice. Indeed, pancreas-deficient *Bmal1* mice develop diabetes mellitus,[77] and knockout of *Clock* in cardiomyocytes alters the normal circadian rhythm of cardiac output, heart rate, and BP.[7] Future studies using kidney-deficient clock genes will be critical to our understanding of how the circadian clock regulates renal function.

In addition to the transcriptional and post-translational regulation of the clock mechanism discussed above, microRNAs (miRNAs), which regulate mRNA stability and therefore protein expression, may play a role in the modulation of circadian rhythms.[78] In mammalian cell models, miRNA-192/194 regulates the expression of the *Period* gene family.[79] Overexpression of this miRNA causes a shortened circadian period. Very little is known about post-translational control of clock proteins in the kidney,[80] and the role of miRNAs in the renal circadian clock has not been explored to date. These dynamic processes likely allow fine-tuning of the clock mechanism in a tissue-specific manner.

CONCLUSIONS

Discerning the role of the circadian clock in the kidney has important implications for the design of novel therapies and improvement of existing treatments for renal disease. Numerous trials showed that chronotherapy in the treatment of nondippers is effective in restoring the normal 24-hour rhythm of BP in many patients. Improved use of 24-hour ambulatory BP monitoring could increase identification of nondippers that may benefit from nighttime administration of anti-hypertensive medications. Nighttime dialysis may benefit patients experiencing circadian disruption. To identify those patients most likely to benefit from chronotherapeutic intervention, we must gain a more complete understanding of the mechanism by which the circadian clock regulates renal function.

Acknowledgments

DISCLOSURES

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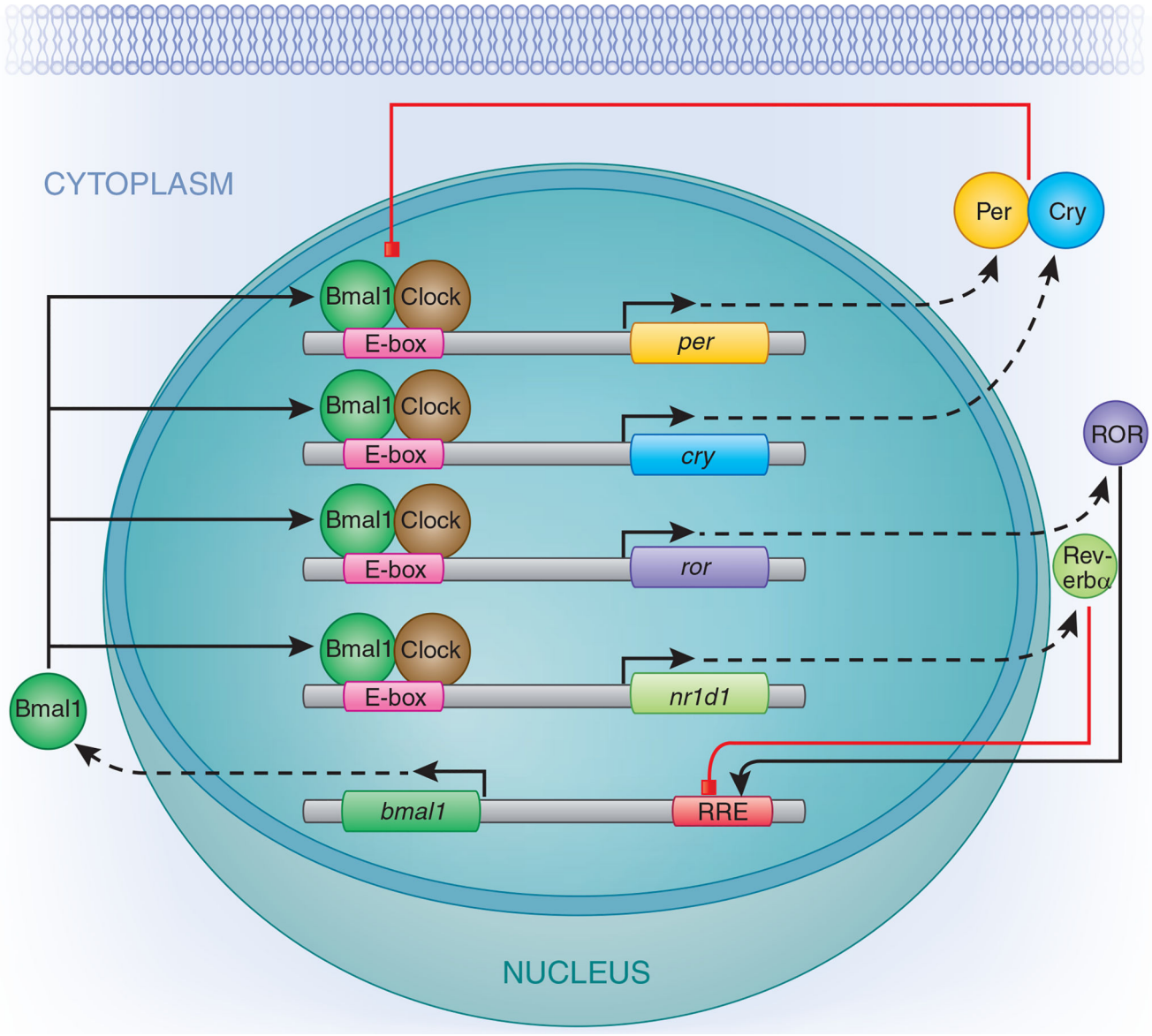

Figure 1.

Transcriptional mechanism of the circadian clock. Bmal1 and Clock heterodimerize to positively regulate expression of the *Period* (*per*) and *Cryptochrome* (*cry*) gene families, as well as the retinoic acid orphan receptor (*ror*) and *Nr1d1* (*rev-erbα*) genes. Per/Cry inhibit Bmal1/Clock action to repress their own transcription, whereas ROR and Rev-erbα mediate opposing action on *bmal1* gene expression. Expression of the Clock protein is constitutive in many tissues. Bmal1/Clock action is mediated through binding of E-box response elements (CANNTG) in the promoters of target genes.

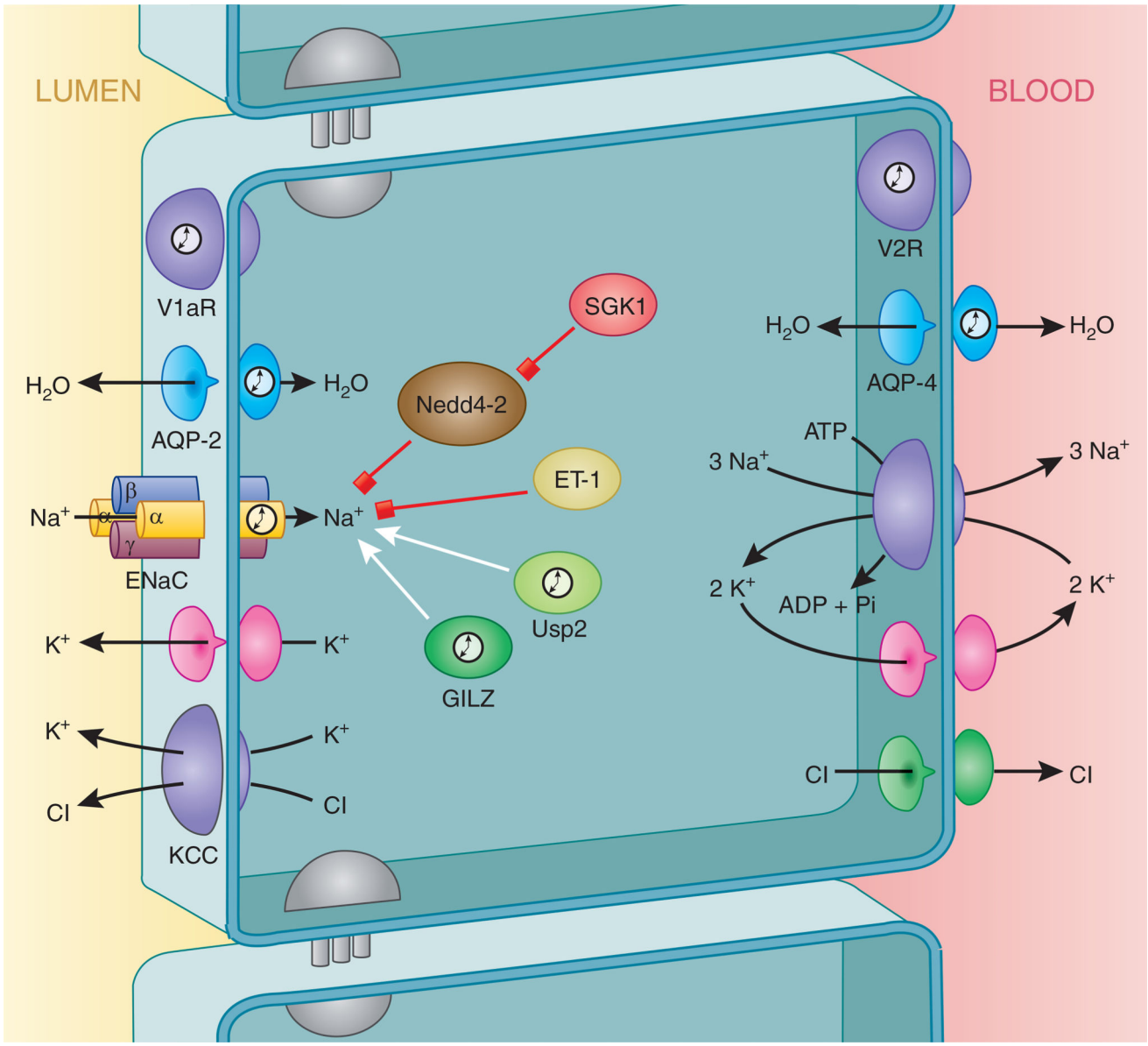

Figure 2.

Mechanisms of sodium, potassium, chloride, and water transport in a cortical collecting duct principal cell. Proteins denoted by the symbol are the products of genes that are expressed in an apparent circadian pattern. Na^+, sodium; K^+, potassium; Cl^-, chloride; H_2O, water; ENaC, epithelial sodium channel; GILZ, glucocorticoid-induced leucine zipper protein; Usp2, ubiquitin-specific protease 2; SGK1, serum and glucocorticoid-regulated kinase; ET-1, endothelin-1; Nedd4–2, neural precursor cell expressed, developmentally downregulated gene 4-like; V1aR, vasopressin 1a receptor; V2R, vasopressin 2 receptor.

Table 1

Clock-controlled genes in the kidney

Gene	Function	RNA Source	Reference
Dec1	bHLH transcription factor	Whole kidney	59
Dec2	bHLH transcription factor	Whole kidney	59
Npas2	bHLH transcription factor	Whole kidney	59
Dbp	Albumin Dsite binding protein	Whole kidney	59
Cldn4	Claudin 4, Tight junction protein	Whole kidney	60
E-cadherin	Adherens junctions	Whole kidney	60
Kid-1	Zn finger transcription repressor	Whole kidney	63
Cldn8	Claudin 8, Tight junction protein	DCT, CNT	61
Mapre2	Microtubule associated protein	DCT, CNT, CCD, whole kidney	61
Ptges	Prostaglandin E synthase	DCT, CNT	61
Tfrc	Transferrin receptor	DCT, CNT, CCD, whole kidney	61

bHLH, basic helix-loop-helix; DCT, distal convoluted tubule; CNT, connecting tubule; CCD, cortical collecting duct.

Table 2

Clock-controlled transport genes in the kidney

Gene	Function	RNA Source	Reference
Slc9a3 (NHE3)	Sodium/hydrogen exchange	Whole kidney	66
Gilz	Leucine zipper protein/regulation of sodium transport	DCT, CNT, CCD. Whole kidney	61
Usp2	Ubiquitin specific protease/regulation of sodium transport	DCT, CNT, CCD. Whole kidney	61
V1aR	Vasopressin receptor/regulation of water balance	DCT, CNT, CCD. Whole kidney	61
V2R	Vasopressin receptor/regulation of water balance	DCT, CNT, CCD. Whole kidney	61
Slc6a6	Taurine transporter	CCD	61
Slc6a9	Glycine transporter	DCT/CNT	61
Aqp2	Water channel	CCD	61
Aqp4	Water channel	CCD	61
Scnn1a (αENaC)	Alpha subunit of epithelial sodium channel	Cortex, outer medulla and inner medulla	65

DCT, distal convoluted tubule; CNT, connecting tubule; CCD, cortical collecting duct.