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Full Reviews

Circadian glomerular function: from physiology to molecular and therapeutical aspects

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ABSTRACT

Life on earth is rhythmic by essence due to day/night alternation, and many biological processes are also cyclic. The kidney has a special role in the organism, controlling electrolytes and water balance, blood pressure, elimination of metabolic waste and xenobiotics and the production of several hormones. The kidney is submitted to changes throughout 24 h with periods of intense activity followed by calmer periods. Filtration, reabsorption and secretion are the three components determining renal function. Here, we review circadian changes related to glomerular function and proteinuria and emphasize the role of the clock in these processes.

Keywords: circadian clock, glomerular filtration, kidney, proteinuria

INTRODUCTION

Alternation of day and night imposes rhythms on all forms of life, and hence, a metabolic challenge for all organisms with periods of intense activity and feeding, and periods of rest and fasting. Task repetition over 24 h allows anticipation of specific events such as food intake and its associated burden on downstream metabolism. But anticipation is made possible only by the presence of an intrinsic timer and a system that will prepare the organism for specific tasks at a determined time point. Circadian clocks have been described in almost all organisms from unicellular archeobacteriae to humans. Molecular aspects of the circadian clock were identified several years ago and encompass several transcription factors (BMAL1, CLOCK, NPAS2) regulating transcription of their own repressors (PERs and CRYs). This autoregulatory feedback loop takes about 24 h to complete and further regulates up to 10–20% of the transcriptome (see [1] for review).

During evolution, the kidney was forced to adapt to highly challenging conditions. If initially the kidney was considered as an almost purely waste excretory organ, terrestrial adaptation pushed to develop waste recycling, tubular reabsorption of solutes and urine concentration ability [2]. Thus, the move away from the initial ocean rendered the kidney more dependent on day/night cycles and anchored renal function in circadian variations.

Renal function is a result of filtration, reabsorption and secretion. All of these functions have been shown to cycle over 24 h, but debates about the underlying regulatory process remain. The discovery of the molecular clock allowed better characterization of some of these processes and shed new light and thoughts on how circadian rhythms may be induced.

Glomerulus and tubules express all components of the molecular clock. Molecular clocks have been described even in the invertebrate fly *Drosophila* which has no glomerulus, but instead has a high-capacity transporting epithelia in their kidney equivalent, called Malpighian tubules [3]. The real roles of these clocks in the kidney, especially in tubular functions, have just started to be unveiled and have recently been reviewed [4]. In the present review, we focus on the roles of the clocks in renal filtration and illustrate the possible causative factors influencing them. We first review evidence of the circadianicity of the glomerular filtration rate (GFR), try to identify the causes of this rhythmicity by analysing the putative cyclicity of the major known factors influencing GFR and search for evidence of a relationship between disturbance of circadian GFR and pathologies, including renal insufficiency and

proteinuria. Of note, particular caution should be exerted regarding the human studies presented here as most of them have been conducted on small populations from various ethnic origins and may not be applicable in general.

Is GFR circadian?

Time-dependent change in GFR has been described in different species and its amplitude depends on environmental conditions. The most extreme example is probably found in hummingbirds. These birds face dramatic changes between day, during which they ingest an important amount of water, and night, where they are exposed to water restriction. Hummingbirds solved this quandary by regulating their water balance through varying GFR, decreasing GFR in case of water restriction and even shutting down GFR completely at night [5]. This regulatory pattern might be mediated by ADH, regulating directly pre-glomerular arteriolae [6, 7].

Several authors have addressed the question of whether GFR is cyclic in humans. A state-of-the art physiological study was performed by Koopman *et al.* [8], who studied 11 normal volunteers under standardized conditions (identical small meal every 3 h, bed rest) and measured GFR by inulin clearance and effective renal plasma flow (RPF) by *p*-aminohippurate clearance. The amplitude of GFR variation was 36 mL/min over 24 h, representing a 33% variation over the mean. The peak GFR was reached between 4 and 5 p.m. and the lowest point was between 2 and 3 a.m. When RPF was measured, these authors found similar variations with a 214 mL/min amplitude (34% over the mean) and a peak slightly shifted to 7–8 p.m. and a nadir at 6–7 a.m. compared with those of GFR. Due to the shift between GFR and RPF, the filtration fraction (FF = GFR/RPF) also presented an oscillatory rhythm with a peak at 11 a.m. and a nadir between 1 and 2 a.m. Compared with inulin clearance, endogenous creatinine clearance showed smaller amplitude, if any, and shifted peak and nadir. Of note, plasma creatinine levels showed only small circadian variations (±8 μmol/L or 9.4% over the 24 h mean). Blocking of tubular creatinine secretion by cimetidine induced a perfect fit of endogenous creatinine and inulin clearances, showing the importance of nocturnal secretion of creatinine in humans [9]. If this variation of GFR over 24 h seems to be robust in young individuals, it might be blunted in older patients [10] or at least under particular conditions. Indeed, when compared with young hypertensive, older hypertensive subjects had blunted GFR oscillations as measured by creatinine clearance [11].

Noteworthy, at least one study did not find any cyclicity of GFR as measured by both endogenous creatinine and cystatine C [12]. Further studies comparing 24 h changes in cystatin C levels and inulin clearance are certainly awaited in order to conclude.

Altogether, the data published so far show that GFR displays robust circadian changes in humans. Creatinine clearance might not be a reliable marker of GFR rhythmicity, due to its strong dependence on proximal tubule secretion, itself highly upregulated at night.

Factors potentially involved in circadian variations of GFR

GFR depends on alterations in the ultrafiltration coefficient (K_f) and on the transcapillary hydrostatic pressure difference (difference between capillary and Bowman's space hydrostatic pressure or Δhydrostatic pressure) and on the transcapillary oncotic pressure difference (difference between capillary and Bowman's space oncotic pressure or Δoncotic pressure) as follows [13]:

$$\mathrm{GFR} = K_f^{*}(\Delta \mathit{hydrostatic\,pressure} - \Delta \mathit{oncotic\,pressure})$$

Of all the determinants of GFR, the glomerular capillary hydrostatic pressure is probably exposed to the most intense daily fluctuations. Indeed, pressure in the glomerular capillaries is itself influenced by many factors of which systemic blood pressure, renal blood flow and changes in afferent or efferent arteriolar resistance are the most prominent. Arteriolar resistance is partially under intrinsic myogenic control, but can also be influenced by other factors including angiotensin II, norepinephrine, renal prostaglandins, atrial natriuretic peptide (ANP), vasopressin and tubuloglomerular feedback (Table 1). Therefore, if any one of these factors is affected by circadian variation, rhythmicity of GFR can be expected. Alternatively, direct control of GFR by the molecular clock—acting on the myogenic tonus of efferent arteriolae for instance—could be envisioned, but was so far not demonstrated.

If direct measurement of capillary hydrostatic pressure over 24 h was never performed, some of the factors influencing it are known to change over the day and are reviewed hereafter.

Systemic blood pressure displays well-established circadian rhythm with clear dipping during the inactivity phase. But its direct involvement in changing capillary hydrostatic pressure over 24 h is probably low: Voogel *et al.* [16] have demonstrated that circadian changes of GFR are probably independent of systemic blood pressure.

The sympathetic nervous system may also affect the GFR differentially between the sleep and awake cycle. It has been shown in healthy participants, for instance, that sympathetic nervous activity decreases during sleep [17]. Using microneurography, Somers and colleagues showed that burst frequency and burst amplitude decreased during phases of the sleep cycle, except for the rapid eye movement sleep. These variations in sympathetic nervous activity might directly and/or

Table 1. Factors potentially involved in circadian variations of GFR

Factors influencing GFR	Circadian?
Filtration coefficient	Not known
Capillary hydrostatic pressure	Not known
Systemic blood pressure	Yes [14]
Renal blood flow	Yes [8]
Regulation of afferent and efferent arteriolar resistance	Yes [15]
Sympathetic system	Yes [15]
Hormones (renin, angiotensin II, PGE2, ADH, etc.)	Yes [16]
Tubuloglomerular feedback	Not known
Bowman's space hydrostatic pressure	Not known
Capillary oncotic pressure	Not known
Bowman's space oncotic pressure	Not known

indirectly affect GFR since progressive stimulation of the renal sympathetic nervous system leads to stepwise activation of renin release, renal sodium absorption and decrease of GFR, as demonstrated in dogs [15]. Using lower body negative pressure as an indirect way of stimulating the sympathetic nervous system, we were able to confirm these data in humans [18]. However, the effect of this stimulation on the GFR could not be measured during this experiment. The effect of the sympathetic nervous system on the GFR was studied in seven kidney transplanted patients considered as denervated with stable renal function, and compared with 10 healthy volunteers [19]. Normal variations of the GFR, measured by inulin clearance, were observed in all transplanted patients except for the one with the lowest function. This suggests a minor role of the sympathetic nervous system in the regulation of GFR, but would need further confirmation in other denervated patients.

Several hormones are highly cyclic during 24 h and may influence GFR through their action on hydrostatic pressure. Among them, the renin–angiotensin–aldosterone system is of particular importance, regulating tightly efferent arteriolar tonus. Sleep/awake cycles have a strong influence on plasma renin activity with increase in both frequency and amplitude of the oscillations in healthy young men [20]. Aldosterone is related to plasma renin activity during sleep but seems to be associated to cortisol pulses during awake periods [21]. In 10 healthy volunteers studied under controlled settings (including position, diet and sleep, but normal light/dark cycles) and during two periods, at baseline and during a prolonged bed rest, circadian fluctuations of melatonin, plasma renin activity, aldosterone and cortisol could be detected [22]. Peak secretion occurred at night in the following order: melatonin, PRA, aldosterone and cortisol. The simultaneous measurement of hormones of the renin–angiotensin system and melatonin is of interest since there seems to be an interaction of angiotensin with melatonin synthesis and release, and both may interfere with circadian rhythms [23]. Of note, progressive impairment of renal function is associated with impairment of the endogenous melatonin rhythm [24].

Prostaglandins exert counter-regulation to angiotensin effect and are of utmost importance for GFR regulation, especially in aging patients. Intrarenal synthesis of prostaglandins is dependent on several enzymatic reactions, mainly driven by the cytochrome P450 family. It has been shown that urine prostaglandin excretion is circadian with higher levels measured during the day [25]. We have shown that the metabolism of prostaglandins, especially of the precursor 20-HETE, was disturbed in mice in which the molecular clock is disrupted, affecting sodium balance and blood pressure [26]. Its role on GFR however has not been studied in detail in this study.

Unlike the hummingbird, there seems to be no circadian rhythm of vasopressin release in humans. Using copeptin, the C-terminal vasopressin precursor fragment, Darzy *et al.* [27] found no consistent circadian rhythm in seven healthy young subjects. An earlier study, however, with direct measurement of vasopressin (AVP), identified diurnal changes in plasma AVP with nocturnal increase occurring early during the night [28]. Consistently, an abnormal diurnal variation of vasopressin has been found in 29 patients with nocturnal polyuria [29]. A more recent study in 15 children with nocturnal polyuria resistant to desmopressin found that the circadian rhythms for both sodium excretion and for GFR were lost, suggesting that other factors are involved in the control of the GFR rhythmicity [30]. In another study looking at the effect of sleep deprivation on 24-h AVP concentrations, no difference was found between the baseline period and after sleep deprivation, both periods showing no significant circadian variability of AVP concentration [31].

Finally, if the above-described factors are mainly determinants of the capillary hydrostatic pressure, oncotic pressure might also be contributing to circadian changes of GFR. Synthesis and concentration levels of several plasma proteins, starting with albumin, have a strong circadian rhythm that may ultimately lead to changes of plasma oncotic pressure, even if this was never directly measured over 24 h [32].

Circadian GFR and pathologies

Unlike blood pressure where clear epidemiological data of adverse outcomes associated with higher night-time blood pressure exist [33], similar data regarding GFR could not be retrieved in the literature. This might be secondary to the difficulty of obtaining split (day/night) measures of GFR, compared with the relative convenient availability of ambulatory blood pressure measurement. However, a clear correlation between night/day alternation in mean arterial blood pressure and in GFR could be demonstrated in diabetic nephropathy [34]. Moreover, epidemiological data indicate that alteration of the blood pressure dipping pattern might be associated with poorer renal outcome, as assessed by eGFR and proteinuria [35].

Regarding blood pressure and disruption of circadian rhythm, Fukuda and colleagues postulated that impaired daytime sodium excretion could cause a night-time increase of blood pressure in order to increase pressure natriuresis and hence keep sodium balance [36–38]. Interestingly, creatinine clearance has been shown to be associated with decreased dipping and night-to-day ratio of sodium excretion, suggesting that patients with impaired renal function need higher night-time blood pressure to excrete sodium and hence a longer time to achieve a dipping pattern [14]. The same group subsequently showed that sodium restriction or the use of diuretics could restore a dipping pattern of blood pressure in patients with essential hypertension [36, 39]. In a sample of 20 patients with chronic kidney disease, the angiotensin II receptor blocker olmesartan could also restore a dipping pattern of BP [40]. This finding was attributed to enhanced sodium excretion during daytime. However, other mechanisms secondary to changes of renal haemodynamics such as reduced filtration fraction, which are well-described effects of blockers of the renin–angiotensin system, may be implicated [41, 42]. Chronotherapy has been proposed for restoring the dipping pattern of blood pressure. In hypertensive patients on three antihypertensive drugs, patients who were randomized to take one of the drugs in the evening compared with all drugs in the morning had decreased night-time blood pressure [43]. The proportion of dippers was significantly increased in this group. In patients with CKD, the evening dosing of one antihypertensive drug resulted in a

reduced risk of cardiovascular events [44]. These promising results await further confirmation by double-blind controlled trial. These studies have focused on blood pressure circadian changing pattern restoration, but they have not looked at whether renal function was restored, and if so, how this was achieved precisely.

The effect of sleep deprivation on renal function was studied in 10 male and 10 female healthy volunteers [31]. Endogenous creatinine clearance was increased, as well as diuresis and natriuresis. Moreover, night-time blood pressure was higher and nocturnal dipping was blunted with more pronounced effects on men than on women. Hormones of the renin–angiotensin system (renin, angiotensin II and aldosterone) were significantly lower during sleep deprivation, while ANP and vasopressin concentrations were not affected.

Patients with stage 5 renal insufficiency and on dialysis seem to have preserved circadian rhythms of plasma phosphate, calcium and PTH [45, 46]. But if the rhythms of these solutes and hormone were not affected in these patients, other hormones, especially those regulating energy homeostasis, showed strong alteration of their circadian profile. Suneja and colleagues showed in 10 fasting dialysed patients, compared with 8 healthy volunteers, that leptin, PYY and NPY concentrations were markedly elevated, while ghrelin concentrations were lower. Moreover, the 72-h hormonal profiles of these hormones were markedly modified. This pattern of metabolic hormones (high leptin, low ghrelin) was suggested to be anorexigenic, but this was not documented in these patients. However, this pattern could be associated with the elevated blood pressure and with the strikingly increased cardiovascular mortality seen in these patients [47].

Is proteinuria circadian?

Filtration through glomerulus is a complex process [48]. Filtrate has to cross three different layers before reaching early proximal tubules: fenestred capillaries, glomerular basal membranes and slit diaphragm between the podocyte feet. If any of these structures fails, proteinuria generally develops as one of the earliest signs and can lead to life-threatening nephrotic syndrome. However, tubules have strong capacities in reabsorbing proteins and display efficient protein-reabsorbing mechanisms, such as the megalin/cubilin protein reabsorption system. Proteinuria is thus the result of an imbalance between excessive filtration of proteins across glomerulus and/or tubular inability to reabsorb the amount of protein filtered. As filtration across glomerulus follows circadian rhythm and most of tubular functions are oscillating as well, several groups address the possibility of proteinuria being circadian.

Buzio *et al.* [49] found that physiologic protein excretion is circadian and presents a peak which is synchronized with the maximal GFR and the plasma protein peak concentration. Similarly, others identified a peak in urinary protein excretion in the late afternoon [50]. Glycosaminoglycans, which are part of the glomerular basal membrane, showed a circadian urinary excretion rate correlated to GFR in rats [51]. Other tubular proteins, such as NAG, beta-2 microglobulin, have been described with circadian rhythms of their excretion rate closely correlated with urine albumin excretion and GFR [52].

Overt proteinuria seems to display also significant circadian rhythmicity. Out of 17 patients with different types of glomerulopathies and proteinuria, Koopman *et al.* [53] found 13 who displayed circadian proteinuria, with a peak at 4 p.m. and a nadir at 3 a.m., independent of the type of underlying pathology. In further exploration of proteinuria rhythms, the same Dutch group infused inulin and different sizes of dextran to eight nephrotic syndrome patients with preserved renal function and in six normal volunteers. They found that the nephrotic patients presented circadian proteinuria for dextran size bigger than 45 A, in the phase with the rhythm of the GFR [54]. Interestingly, nephrotic patients with inverted sodium rhythms (excreting more sodium at night than in the day, representing about half of the patients) had worse proteinuria and worse prognosis of their underlying disease, as assessed on biopsies [55]. Based on these findings, it was proposed that proteinuria cyclicity could be attributed to both haemodynamic factors and changes in the Sieving index [56].

Role of the molecular clock in GFR and proteinuria

The molecular clock is well established as a strong regulator of expression of RNA, protein, but also as regulator of post-translational modifications. However, data showing a direct implication of the molecular clock in regulation of GFR have not been published so far. Likewise, a role of the molecular clock in controlling tubular reabsorption of proteins, including albumin, is lacking. Conversely, a slight impairment of the diurnal rhythm of some molecular clock components was recently found in a rodent model of renal insufficiency established by 5/6 nephrectomy [57].

Regarding the effect of the molecular clock on the different factors affecting GFR and discussed previously, one of the first questions coming to mind is whether renin production is directly regulated by the molecular clock and thus whether the deletion of the cyclicity of renin may have a direct influence on GFR. This will need to be carefully examined in renin specifically driven Cre-expressing mice crossed with BMAL1 floxed mice.

Likewise, putative rhythmicity at the RNA, protein or functional level of the GBM or slit diaphragm components still needs to be described as well as possible circadian variations of the protein uptake mechanisms taking place in the proximal tubule via the megalin/cubilin system for instance.

In conclusion, circadian variation of the GFR is well established (up to 30% over the 24 h mean) and complex. Numerous factors influencing GFR have been shown to display circadian rhythm, but it seems from the data gathered so far in the literature that none of them can by themselves account for the observed cyclicity. Similarly, filtration and reabsorption of proteins exhibit circadian rhythm but the underlying mechanism is unknown. Despite the description of the different components of the molecular clock >10 years ago, no study has addressed the role of intracellular clocks on GFR and filtration. A new era of study is now wide open and needs manpower and innovative approaches. In a world in which human beings are

more and more exposed to disrupted rhythms and in which renal function deterioration is a major threat, better knowledge of the relationship between rhythms and renal function is avidly needed.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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FULL REVIEW

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Defective metabolism in polycystic kidney disease: potential for therapy and open questions

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is a common genetic disorder characterized by bilateral renal cyst formation. The disease is caused by mutations in either the *PKD1* or the *PKD2* gene. Progress has been made in understanding the molecular basis of the disease leading to the general agreement on ADPKD being a loss-of-function disease. Identification of signalling cascades dysfunctional in the cystic epithelia has led to several pre-clinical studies of animal models using a variety of inhibitors to slow disease progression. These were followed by clinical trials, some of which generated promising results, although an approved therapy is still lacking. Here, we summarize and discuss recent work providing evidence that metabolic alterations can be observed in ADPKD. In particular, we will focus our discussion on the potential role of glucose metabolism in the pathogenesis of ADPKD. These recent findings provide a new perspective for the understanding of the pathobiology of ADPKD and open potential new