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Review Article

Circadian regulation of renal function

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ABSTRACT

The kidneys regulate many vital functions that require precise control throughout the day. These functions, such as maintaining sodium balance or regulating arterial pressure, rely on an intrinsic clock mechanism that was commonly believed to be controlled by the central nervous system. Mounting evidence in recent years has unveiled previously underappreciated depth of influence by circadian rhythms and clock genes on renal function, at the molecular and physiological level, independent of other external factors. The impact of circadian rhythms in the kidney also affects individuals from a clinical standpoint, as the loss of rhythmic activity or clock gene expression have been documented in various cardiovascular diseases. Fortunately, the prognostic value of examining circadian rhythms may prove useful in determining the progression of a kidney-related disease, and chronotherapy is a clinical intervention that requires consideration of circadian and diurnal rhythms in the kidney. In this review, we discuss evidence of circadian regulation in the kidney from basic and clinical research in order to provide a foundation on which a great deal of future research is needed to expand our understanding of circadian relevant biology.

1. Introduction

Circadian rhythms are defined by Merriam-Webster as “being, having, characterized by, or occurring in approximately 24-h periods or cycles.” These rhythms exist in all mammalian tissues throughout the body with as many as 40% of the protein-coding genes displaying oscillatory expression [1]. We have long known that the kidney functions in a pattern that varies according to the time of day, yet we know very little about the mechanisms that control the various functions that follow a diurnal or circadian pattern. In the early 1950's, Mills and Stanbury published evidence that healthy human subjects excrete water and electrolytes in a diurnal pattern independent of daily habits of eating, sleeping and overall activity [2,3]. Such findings were confirmed by Moore-Ede and colleagues in 1977 using squirrel monkeys where they had more tight control of intake [4]. Unfortunately, these studies generated little enthusiasm from the renal community at large until very recently when several studies provided more mechanistic reasons to explore these mechanisms. Furthermore, recent RNA-seq analysis of mouse tissues revealed that the kidney is second only to the liver in the number of genes expressed in a circadian pattern [1]. The current review will focus on the overall evidence for physiological regulation of specific mechanisms along the nephron in the context of our current understanding of circadian control.

The discovery of the so-called “clock” genes as a series of transcription factors expressed in an oscillating loop provides an opportunity for a tremendous amount of new information related to circadian control systems. In general, the molecular clock mechanism consists of a transcription-translation oscillatory feedback loop that involves products of the core clock genes, *Bmal1* (or ARNTL, aryl hydrocarbon receptor nuclear translocator-like protein 1) and *Clock*, that function as transcription factors to drive gene expression in the nucleus of the nucleus. The formation of a Bmal1-Clock heterodimer undergoes

Abbreviations: 3ß-HSD, 3ß-hydroxysteroid dehydrogenase-isomerase; ABPM, ambulatory blood pressure monitoring; Ang II, angiotensin II; ARB, angiotensin receptor blocker; AT1, angiotensin receptor type 1; AT2, angiotensin receptor type 2; ACE, angiotensin-converting enzyme; Agt, angiotensinogen; ADH, anti-diuretic hormone; AQP2, aquaporin 2; AVP, arginine vasopressin; ARNTL or Bmal1, aryl hydrocarbon receptor nuclear translocator-like protein 1; BP, blood pressure; CCB, calcium channel blocker; CK1δ/ε, casein kinase 1 isoforms δ/ε; CKD, chronic kidney disease; CRIC, chronic renal insufficiency cohort; CNT, connecting tubule; CHD, conventional hemodialysis; CCD, cortical collecting duct; *Cry*, cryptochrome; DCT, distal convoluted tubule; ERPF, effective renal plasma flow; ESRD, end-stage renal disease; ET-1, endothelin-1; ENaC, epithelial sodium channel; EPO, erythropoietin; ERß, estrogen receptor ß; GFR, glomerular filtration rate; GC, glucocorticoids; HK-2 cells, human kidney-2/human proximal tubule; HCTZ, hydrochlorothiazide; IMCD, inner medullary collecting duct; NKCC2, Na^+-K^+ − $2Cl^-$ co-transporter; NCC, Na^+Cl^- co-transporter; NHD, nocturnal hemodialysis; OAT3, organic anion transporter 3; OMCD, outer medullary collecting duct; *Per*, period; PRA, plasma renin activity; ROMK, renal outer medullary K^+; *Ren-2*, renin gene; ROR, retinoic acid-related orphan receptor, renin-angiotensin-aldosterone system (RAAS); SGLT2, sodium-glucose co-transporter 2; NHE3, sodium-hydrogen exchanger 3; STZ, streptozotocin; SCN, suprachiasmatic nucleus; TAL, thick ascending limb; ZT, zeitgeber time

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regulation via activation or repression of Bmal1 expression through the retinoic acid-related orphan receptor (ROR) or Rev-ErbA alpha nuclear receptor families, respectively [5]. The Bmal1-Clock heterodimer forms the positive limb of the feedback loop which then binds to the E-box domain of target genes, including core clock genes Period (*Per*) and Cryptochrome (*Cry*). Per and Cry then leave the cell to either perform various physiological actions or they can re-enter the nucleus of the cell via phosphorylation by Casein Kinase 1 isoforms δ/ε (CK1δ/ε) [6,7]. Groundbreaking work from the Gumz lab published in the Journal of Clinical Investigation in 2009 has sparked new interest in circadian control of kidney function. These investigators reported that aldosterone, the most well established regulator of renal tubular sodium handling, controls the epithelial sodium channel via the core clock gene, *Period 1* [8].

This review is generally divided into three major sections. First, we will discuss what is known about the different sections of the nephron and attempt to provide evidence of a possible circadian intervention, at the physiological level determined by renal function, at the molecular level involving the renal circadian clock, or both. Secondly, we will take an integrated look at how the circadian clock regulates nephron function, and the role hormones and peptides play in that regulation. Finally, after taking a look into some of the pathologies that may be associated with impaired rhythmic activity, we will discuss how circadian rhythms can provide possible solutions to these pathologies.

2. Circadian rhythms along the nephron

2.1. The glomerulus

To be filtered by the kidneys, blood must travel to the glomerulus where the nephron begins. The glomerulus consists of a tortuous bundle of blood capillaries located within the Bowman's capsule. These capillaries receive blood from the afferent arteriole, a unique “high pressure” arteriole that also functions as an endocrine organ through release of renin. The glomerular capillaries are unique in their extreme permeability and very high capillary pressure, thus facilitating the passage of fluid into the proximal tubule to begin the formation of urine [9,10]. Blood that is not filtered by the glomerulus leaves the glomerular capillaries via the efferent arterioles. From there blood passes through the peritubular capillaries and vasa recta, before returning to the systemic vasculature through the renal vein.

Multiple studies have shown evidence of circadian variation in glomerular function (Fig. 1). In normal individuals, glomerular

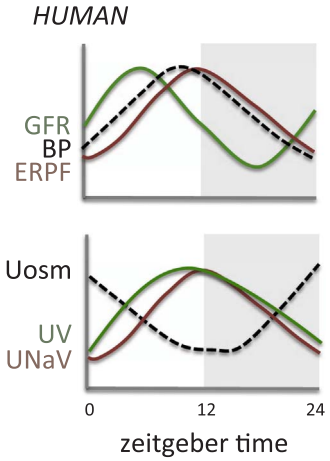

Fig. 1. Estimated circadian rhythms for renal functional parameters. GFR, glomerular filtration rate; BP, blood pressure; ERPF, effective renal plasma flow; Uosm, urine osmolality; UV, urine flow rate; UNaV, sodium excretion.
Adapted from Koopman et al. [11]; Koopman et al. [12]; Mills & Stanbury [2]; Graugaard-Jensen et al. [32]; Kamperis et al. [34]; and Perrier et al. [33].

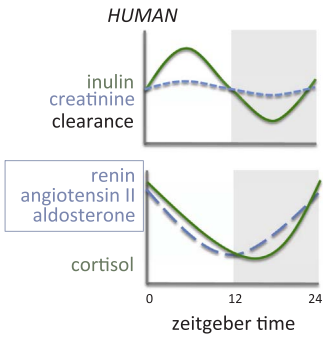

Fig. 2. Estimated circadian rhythms for renal clearance of inulin and creatinine in humans (upper panel) and circulating hormones (lower panel).
Adapted from Gordon et al. [93]; Kala et al. [103]; Hurwitz et al. [92]; Williams et al. [109]; Guignard et al. [117]; Van Cauter et al. [116].

filtration rate (GFR) measured by inulin and creatinine clearance reaches a maximum during the day, peaking around 2–3 p.m., and a minimum in the middle of the night [11–13]. Effective renal plasma flow (ERPF) as measured by p-aminohippurate clearance also shows a circadian rhythm peaking during the day, or active period, although this peak appears to occur later in the afternoon compared to GFR (Fig. 1) [11,12]. As a result, the filtration fraction (GFR/ERPF) also displays circadian rhythmicity. The physiological significance of the adjustments in filtration fraction is unknown, but the rhythm in GFR is presumably commensurate with the need to excrete a larger volume of urine during the active period when consumption of water is also at its highest. It is also relevant to note that the clearance of inulin and creatinine, two important markers used for assessment of GFR, do not have the same level of circadian variation [11] (Fig. 2). This is likely due to the large amount of creatinine secretion that occurs in the proximal tubule and suggests that creatinine clearance is not a reliable way of assessing diurnal variations in GFR.

Diurnal variations can also be seen in the filtered load of water and sodium (Fig. 1) [11]. There is also circadian variation seen in urinary albumin and ß$_2$-microglobulin excretion with a phase similar to GFR in normal individuals [11]. Collectively, these observations demonstrate that parameters used as biomarkers for glomerular function such as creatinine could potentially change depending on the time of day the measurements are taken. They also suggest an interaction between the molecular clock mechanism and the glomerulus. A study by Huang et al. noted that in male Wistar rats, the glomerular capillaries express the core clock protein Bmal1 and clock output protein, D site albumin promoter binding protein (Dbp), and that these expression levels change at different times of the day [14]. A list of the expression level acrophases and nadirs of different clock and clock-controlled genes throughout the nephron in whole rodent kidneys is provided in Table 1. Although these results suggest an association between circadian clock proteins and the diurnal variation in renal function, more work is needed to elucidate the localization of other clock proteins within the glomerulus as well as afferent and efferent arterioles to determine what impact each clock gene may have on regulating glomerular function. Fig. 3 summarizes some of what is known about specific clock genes impacting specific transporters along the nephron, although very little is specifically known about these relationships.

2.2. The proximal tubule

The proximal tubule reabsorbs approximately 65% of the glomerular ultrafiltrate, including nearly all of the amino acids and glucose. This fraction stays quite consistent by adjusting proximal reabsorption of solutes and water in response to the variations in GFR in order to keep fractional reabsorption constant; this intrinsic property of the kidney is known as glomerulotubular balance [15–17]. Glomerulotubular balance involves the full range of co-transporters and