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Circadian Clock Genes in Diabetic Kidney Disease (DKD)

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Abstract

Purpose of Review: The purpose of this review is to provide a brief summary about the current state of knowledge regarding the circadian rhythm in the regulation of normal renal function.

Recent findings: There is a lack of information regarding how the circadian clock mechanisms may contribute to the development of diabetic kidney disease. We discuss recent findings regarding mechanisms that are established in diabetic kidney disease and are known to be linked to the circadian clock as possible connections between these two areas

Summary: Here we hypothesize various mechanisms that may provide a link between the clock mechanism and kidney disease in diabetes based on available data from humans and rodent models.

Keywords

circadian rhythm; renal function; HIF; shift work; BMAL1

Introduction

The circadian clock is a network of interconnected transcription- translation feedback loops, in which translated circadian proteins inhibit their own mRNA transcription to generate cell autonomous and self-sustaining transcriptional circadian oscillations that contribute to the regulation of most physiologic functions[1, 2]. The core mechanism is comprised of several transcription factors that participate in a transcription-translation feedback loop (Figure 1). In mammals the main feedback loop is activated by a heterodimeric transcription activator Brain and muscle ARNT-like 1 (BMAL1 or ARNTL) and the Circadian Locomotor Output Cycles protein Kaput (CLOCK). BMAL1-CLOCK heterodimers trigger the transcription of

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Conflict of Interest

Olanrewaju A. Olaoye, Sarah H. Masten, Rajesh Mohandas, and Michelle L. Gumz declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

a wide range of circadian clock-controlled genes (CCGs), identified as the ‘Period’ and ‘Cryptochrome’ families of genes (PER1/PER2/PER3 and CRY1/CRY2 respectively). PER/CRY heterodimers contribute to the inhibitory feedback loop to decrease the activity of BMAL1-CLOCK. An ancillary loop involving nuclear receptors acts as an additional important feedback mechanism controlling BMAL1 transcription. This complex network is ubiquitously expressed within central nervous system and peripheral tissues including the kidneys[3–5]. An analytical study of transcriptomes of 12 adult mouse organs showed approximately 43% of all protein coding genes in the genome demonstrated circadian oscillations in at least one of the organs tested[6]. Notably, kidney was second only to the liver in terms of total number of circadian transcripts (approximately 13% compared to 16%) supporting significant presence of circadian lock activity in renal cells. Other studies also show that many circadian target genes are organ-specific and are related to tissue-specific functions[7, 8].

Part I. Circadian rhythms in kidney function

Circadian Rhythm and the Kidney Glomerulus

The primary functions of the glomerulus include the selective ultrafiltration of plasma and clearance of small solutes, which is measured by the glomerular filtration rate (GFR). Early studies in human subjects maintained on bed rest, normal sleep/wake as well as light/dark cycles, and identical standardized meals every 3 hours showed that there was a clear circadian pattern to GFR[9],. The GFR measured using inulin clearances was highest during the day (122 ml/min) and lowest at night (86 ml/min). The variations in GFR likely reflect changes in renal plasma flow since the clearance of p-amino-hippurate showed a similar pattern and amplitude. Urinary albumin and β_2-microglobulin excretion were also noted to have a circadian rhythm in-phase with the GFR rhythm. Although very little is known about circadian dysrhythmia leading to glomerular dysfunction, proteinuria in patients with nephrotic syndrome has been observed to follow a circadian rhythm[9, 10]. However, protein excretion is independent of GFR rhythm with peak excretion around 4 pm and almost no protein excretion around 3 am [11].

Circadian Rhythm and Renal Tubules

Following selective ultrafiltration through the glomerulus, renal tubules have the important job of reabsorbing the essential components of the filtrate, while augmenting elimination of non-essential toxic and non-toxic waste products by actively secreting these into the final urinary excreta. The proximal tubule, the kidney power house in this regard, performs the bulk of reabsorption, whereas the distal tubule, along with the collecting tubule, does the fine tuning and finalizes the urine composition. Most renal functional rhythms have similar kinetics with peaks and troughs corresponding to periods of maximal and minimal behavioral activity, referred to as active and inactive phases, respectively[12]. For humans, active phase is generally during the daytime and the inactive phase during nighttime, whereas the reverse is the case in the rodent models used for biomedical research.

Urine volume, electrolyte excretion, and blood pressure all exhibit circadian variation. A normal circadian blood pressure pattern is associated with a 10–15% decrease in blood

pressures at night called a ‘dipping” pattern. We have shown that the α subunit of the epithelial sodium channel (αENaC) exhibits a circadian pattern of expression and *Period 1*-deficient mice have altered expression of αENaC and develop salt-sensitive, non-dipping hypertension[13, 14]. We have also shown that Period 1 regulates the expression of other sodium handling genes in the kidney[15–17]. Transcriptome-wide studies and targeted gene-specific analyses have revealed rhythmic expression of other genes important in salt and water balance including aquaporins, urea transporters and potassium channels[18–21]. Consistent with a critical role for the circadian clock in the regulation of renal gene expression, genetic inactivation of the *Clock* gene leads to notable changes in the kidney transcriptome [22, 23].

The most abundant protein in human urine is uromodulin (also known as Tamm-Horsfall protein). Uromodulin has been identified as a susceptibility gene for a number of kidney diseases and it has been specifically linked to diabetic kidney disease [24],[25]. Uromodulin is produced in the thick ascending limb and appears to play a role in regulating renal sodium handling, sodium-sensitivity, and forming a protective coating in the thick ascending limb of the loop of Henle [26]. It is not clear if uromodulin excretion displays a circadian rhythm, but its urinary levels are observed to correlate with urine volume[27] which exhibits a clear circadian rhythm. Uromodulin was recently identified as a BMAL1-target gene exhibiting differences in expression between 10 am and 10 pm in male mice[28] (see Supplemental Table 4)).

Circadian Rhythm and Renal Interstitium

Advanced DKD is characterized by interstitial inflammation and fibrosis. CLOCK may play a role in prevention of renal fibrosis and parenchymal damage. Following unilateral ureteral obstruction in a CLOCK-null mice, increased renal parenchymal damage and fibrosis were observed, suggesting that the circadian clock plays a role in regulating renal fibrosis[29] possibly by inhibiting transforming growth factor-β-cyclooxygenase 2 (TGF-β-COX2) pro-fibrotic axis in the kidney.

Circadian Rhythm and Renal Neuro-Hormonal System

External cues, including light, food intake, and circulating hormones, determine the periodicity of [(i.e. ‘entrain’)] the circadian oscillations in the kidney. Aldosterone, a mineralocorticoid hormone secreted by the adrenal glands, plays a significant role in the maintenance of extracellular sodium homeostasis and control of blood pressure in part by regulating the epithelial sodium channel (ENaC), the principal sodium channel present on the apical side of the principal cells of the renal collecting duct[30]. Plasma aldosterone levels peak in the first half of the active phase, in parallel with GFR rhythms and filtered sodium load[31]. Plasma aldosterone is significantly increased, and circadian aldosterone oscillations significantly reduced, in mice deficient in CRY1 and CRY2. Analysis of the circadian transcriptome in the adrenal glands of these mice detected an increase in expression of the aldosterone biosynthetic enzyme 3β-hydroxysteroid dehydrogenase/delta 5-to-4 isomerase type 6 (HSD3B6). Functional defects in CRY1/2 knockout mice included significantly elevated plasma aldosterone levels coupled with salt-sensitive hypertension and non-dipping pattern of arterial blood pressure[32].

PER1, one of the core clock components, has been demonstrated to positively regulate aldosterone synthesis in an adrenal cell line and plasma aldosterone levels in-vivo in the 129/sv strain of mice[33]. PER1-null mice on a C57Bl/6 background, under high salt and mineralocorticoid treatment conditions, develop a non-dipping form of hypertension[13, 14]. PER1 has also been shown to control the transcription of the genes encoding several key proteins involved in sodium reabsorption along the nephron (including α-ENaC, NCC, kinases WNK1 & WNK4, NHE3, SGLT1) as well as several components of the endothelin axis[34–36, 17, 37].

Emerging Concepts in Circadian Renal Function

In addition to the classic transcriptional mechanism of the circadian clock, translation occurs in a rhythmic fashion as has recently been described [38]. In the mouse liver, peak ribosome biogenesis and polysome formation occurred in the middle of the active phase, presumably because the circadian clock coordinates the energy consuming process of protein synthesis with energy production in these cells[39, 40]. Ribosomes from murine kidneys have been profiled to identify rhythmically translated mRNAs in the kidney. This compelling study demonstrated that nearly 10% of all detected transcripts were translated in a circadian pattern. [38]. These findings demonstrate that circadian rhythms in function likely relate to rhythmic changes in mRNA levels, translation, and protein expression.

When correlating circadian translation with functional circadian oscillations in renal function, another level of complexity to consider is the effect of post-translational modifications. Such modifications can affect protein stability, subcellular localization, protein-protein interactions and protein function. The total levels of Na-Cl cotransporter (NCC, encoded by the SLC12A3 gene), which controls sodium reabsorption in the distal convoluted tubule (DCT), do not appear to exhibit circadian oscillations but the active phosphorylated form does[41, 42]. Recent global analysis of the circadian phosphorylome and acetylome in the mouse liver revealed approximately 20,000 phosphorylation sites within 4,400 liver proteins, with approximately 25% being regulated in a circadian manner. Of the 1,000 acetylation sites found in the liver proteome, approximately 13% demonstrate circadian oscillations, particularly those involved in the urea and the tricarboxylic acid cycles in the metabolism of amino acids and lipids[43]. It remains to be seen whether post-translational modification of proteins plays a similar role in circadian oscillations of renal function.

Another emerging area concerns the role of circadian rhythms in systemic and renal oxygen levels. In mice, renal oxygen levels can affect the intrinsic renal circadian clock by inducing circadian oscillations in the levels of hypoxia-inducible factor 1α (HIF1α)[44]. The nuclear levels of HIF1α in the kidney oscillated, with a peak in the first half of the active phase. The mechanism appears to be suppression of mTORC1 signaling by the acid load (e.g. lactate) generated during hypoxia [45].

Part II. Potential Role for Circadian Rhythm Dysregulation in DKD

Evidence from Rodent Models and Humans

Accumulating evidence from rodent and human studies indicates that circadian disruption is prevalent in diabetes[46]. This topic has been reviewed in depth recently[47]. One example is that altered circadian expression of clock genes in the kidney has been shown in a rat model of diabetes induced by streptozotocin[48]. Single nucleotide polymorphisms in BMAL1 and CLOCK have been linked to type 2 diabetes in humans[49, 50]. Shift work and chronic circadian disruption appears to cause increased risk for diabetes and other cardiometabolic disorders[51]. Consistent with these genome wide association and epidemiological studies, mechanistic evidence from circadian mutant mouse models supports a connection between the molecular circadian clock and diabetic disorders. Bass and colleagues demonstrated that BMAL1 and Clock mutant mice both develop a diabetic phenotype and that specific disruption of the pancreatic β-cell circadian clock leads to diabetes[52]. The connection between the clock and diabetes is bidirectional, as has been demonstrated by the work of Gong and colleagues using the db/db mouse model[53–55]. The db/db mice exhibit circadian dysfunction in the form of non-dipping hypertension as well as dysregulated rhythms at the level of individual peripheral clocks.

Diabetic Kidney Disease (DKD)

Diabetic kidney disease (DKD), a major microvascular complication of both type 1 and type 2 diabetes mellitus, continues to be a leading cause of end-stage renal disease in Western nations. Classic diabetic nephropathy is characterized by nodular glomerulosclerosis on histopathology and clinically by progressive decline in renal function often preceded by albuminuria. DKD is associated with an increase in morbidity and mortality, in large part due to an increase in cardiovascular disease. Traditionally, DKD was thought to result from interactions between hemodynamic and metabolic factors resulting in increased intra-glomerular pressures and modification of molecules under hyperglycemic conditions[56]. However, growing evidence indicates that the extent of renal damage in patients with DKD is not completely explained by these factors and the pathogenesis is likely multifactorial, with genetic and environmental factors triggering a complex series of pathophysiological events[57, 58]. Inflammation is thought to be one of the key pathophysiological mechanisms responsible for DKD. The components of the diabetic milieu act on the kidneys to activate diverse intracellular downstream signaling cascades, leading to activation of several inflammatory pathways to drive mesangial hypertrophy and deposition of collagen IV & fibronectin. Activation of these signaling pathways results in infiltration by circulating inflammatory cells, thus amplifying and perpetuating the inflammatory process in the kidney. Hypertension, present in almost 65% of the diabetic population,[59] provokes additional injury resulting in the perfect storm of accelerated progressive kidney disease[60, 61].

Potential Effect of Circadian Dysrhythmia on Diabetic Kidney Disease

A non-dipping blood pressure pattern is prevalent in both type 1[62] and type 2[63] diabetics and corresponds to increased albuminuria[64]. Administration of at least one antihypertensive medication at night restores dipping status and improves clinical outcomes

in patients with diabetes[65]. While these observations provide some support for dysfunction of the circadian rhythm in DKD, the molecular mechanisms underlying these defects remains to be elucidated. Below, we speculate as to possible mechanisms involving BMAL1/CLOCK, select clock target genes, and hypoxia signaling that may contribute to the clock dysfunction in DKD.

BMAL1 has been described as the main indispensable component of the core clock machinery[66]. BMAL1-null mice have a multitude of mild-to-severe metabolic alterations including impaired metabolism of glucose[67] and fatty acids[68]. Potential effect of circadian dysfunction from BMAL1 deficiency or malfunction might pave the way for impairment of glucose metabolism, a significant substrate contributor to the complex processes leading to DKD development. As discussed earlier, an optimally functioning CLOCK-driven circadian rhythm prevents renal parenchymal damage and fibrosis[29]. Thus, CLOCK deficiency or dysfunction may lower the threshold for development of microvascular disease and fibrosis or accelerate the progression of DKD.

There are potential effects of circadian dysrhythmia in DKD that may be associated with hypoxia inducible factors (HIF). The connection between hypoxia signaling, HIF1α, and the circadian clock is well-established (see[69] for review). Likewise, growing evidence supports a role for HIF signaling in diabetic kidney disease[70–72]. Indeed, as shown in Figure 2, HIF1α is a clear example of a clock-controlled gene in the kidney (data derived from CircaDB[73]). It is therefore tempting to speculate that loss or dysregulation of clock-mediated control of HIF1α function may be related to development of DKD.

We queried whether other genes, which were linked to DKD via genome wide association studies, are themselves circadian clock target genes, similar to HIF1α. Based on recent evidence [74] [75], we selected several DKD genes and queried CircaDB as well as available transcriptomic data [28][17][22], to look for evidence of circadian rhythmicity. Several genes met this criteria: as discussed above, uromodulin fits in this category since it is a BMAL1 target gene[28] and is also associated with kidney disease in Type 1[76] and Type 2 diabetics [24]. Angiotensin converting enzyme (ACE) is a well-established circadian clock target gene (CircaDB) and polymorphisms in this gene are associated with DKD development in Type 2 diabetics[77]. Another interesting link between circadian rhythms and DKD susceptibility genes is Slc12a3, encoding the NaCl cotransporter, which has been linked to DKD[75] and the clock [41, 42, 17].

Summary and Future Directions

It is clear that the circadian clock, both extrinsic and intrinsic to the kidney, is a key regulator of renal function. Thousands of genes and proteins are under the regulation of the molecular clock mechanism and this likely underlies the known circadian variation to several aspects of renal function. It is less clear what happens to the circadian clock within and outside the kidney in pathophysiological states. Available evidence demonstrates that glucose homeostasis, pro-fibrotic mechanisms, and hypoxia signaling are all subject to regulation by the circadian clock, making these likely suspects for mediating a possible link between circadian rhythm dysregulation and DKD. Future work should be aimed at

understanding whether the clock can be manipulated by pharmacologic or behavioral means in order to improve outcomes in DKD.

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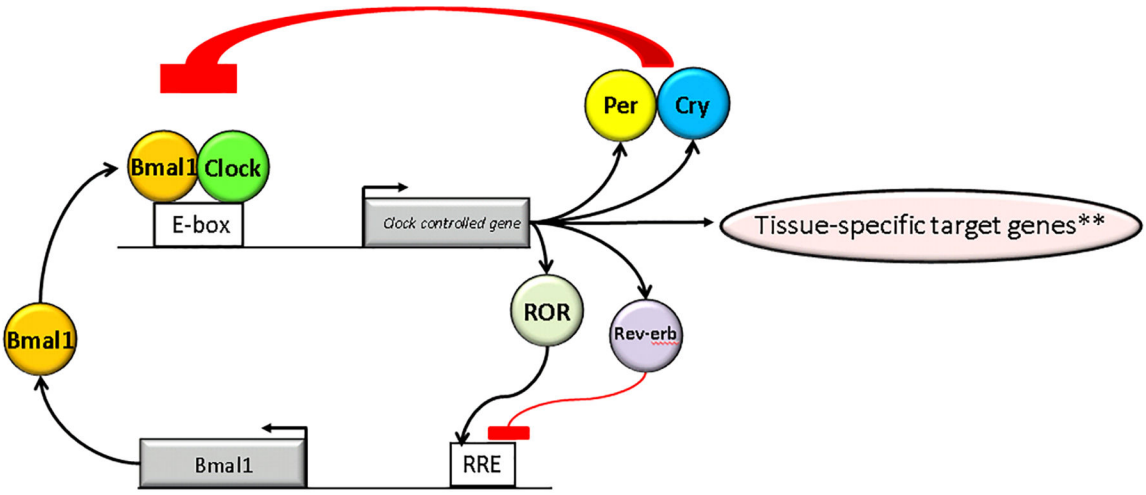

Figure 1.

Simplified Transcription Translation Feedback Loop Mechanism of the Circadian Clock. **Example, HIF1a in the kidney, see Figure 2. Examples also include many genes related to renal sodium handling (see text for discussion).

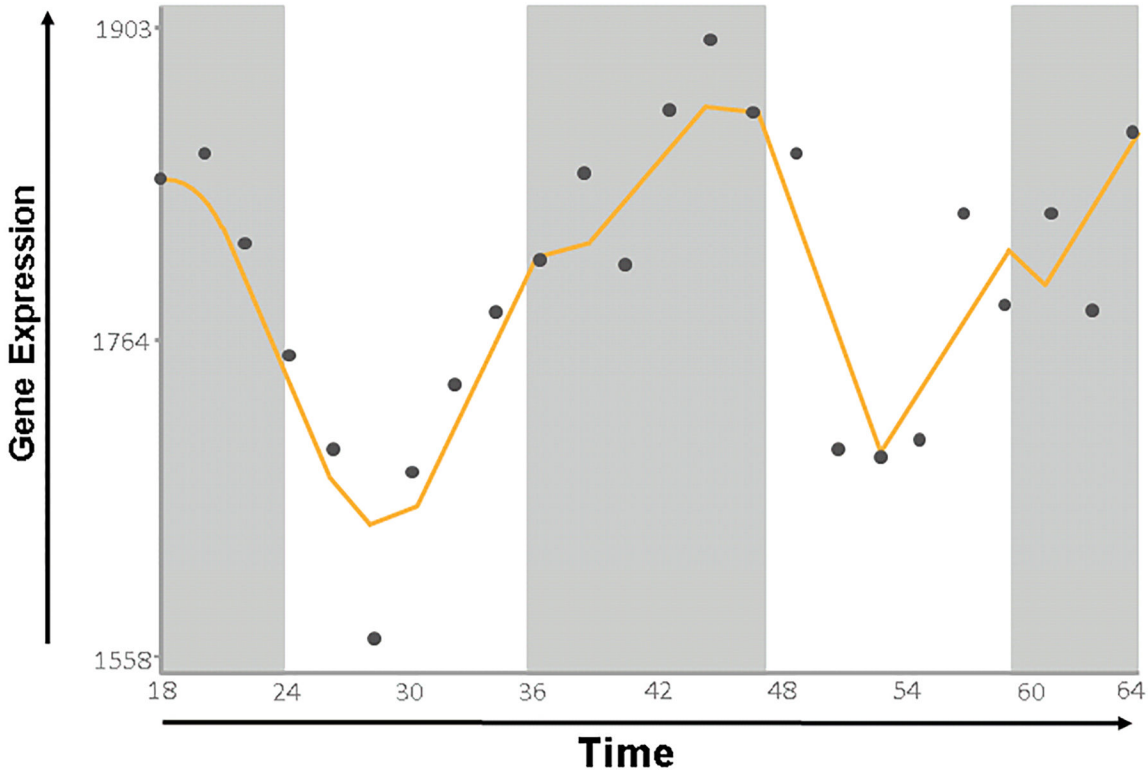

Figure 2.
HIF1a expression in the kidney exhibits a circadian rhythm. Data derived from CircaDB [73]