Published in final edited form as:

Curr Opin Physiol. 2018 October ; 5: 38–44. doi:10.1016/j.cophys.2018.06.002.

RECENT ADVANCES IN UNDERSTANDING THE CIRCADIAN CLOCK IN RENAL PHYSIOLOGY

G. Ryan Crislip^{1,2}, Sarah H. Masten¹, and Michelle L. Gumz^{1,3}

¹Department of Medicine, Division of Nephrology, Hypertension, and Renal Transplantation

²Department of Physiology and Functional Genomics, University of Florida, Gainesville, FL 32610

³Department of Biochemistry and Molecular Biology, University of Florida, Gainesville, FL 32610

Abstract

Accumulating evidence suggests a critical role for the molecular circadian clock in the regulation of renal function. Here, we consider the most recent advances in our understanding of the relationship between the circadian clock and renal physiology.

Introduction

Our bodies are challenged on a daily basis with variables that can potentially change our internal milieu. There are systemic cues that prepare our bodies for these daily events in order to maintain temporal homeostasis. The process by which the body anticipates varying conditions each day is performed by fluctuating mechanisms, which comprise the circadian clock [1]. The circadian field has gained recent attention due to three distinguished scientists (Jeffrey Hall, Michael Rosbash, and Michael Young) being awarded the Nobel Prize in Physiology or Medicine in 2017 for their isolation and characterization of the circadian gene *Period (Per)* in fruit flies [2].

Briefly, the molecular circadian clock is comprised of a series of feedback loops that are primarily controlled by four key proteins (CLOCK, BMAL1, PER, and CRY). This molecular pathway is present in nearly every cell type and organ system in the body. The master clock, located in the suprachiasmatic nucleus (SCN), uses light input to give time cues to peripheral clocks in other cells of the body. Peripheral tissues also possess the ability to sustain their own circadian rhythms to meet individual demands. For a more thorough review on this process, see Partch et al [3]. Not only are circadian genes widespread in the body, they are also found in nearly every organism, ranging from bread mold to humans, and their function allows for adaptation to our planet with a 24-hour light and dark cycle.

Importantly, these circadian genes are highly conserved between mice and humans [4]. It is

Corresponding Author: Michelle L. Gumz, PhD, University of Florida, Department of Medicine, Division of Nephrology, Hypertension, and Renal Transplantation, 1600 SW Archer Road, Box 100224, Gainesville, FL 32610, Telephone: 352-273-6887, Fax: 352-392-5465, Michelle.Gumz@medicine.ufl.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

well established that disruption of sleep and circadian pathways in humans are associated with increased risk for a number of pathologies including cancer and cardiovascular diseases [5,6]. Therefore, considering circadian clock function is imperative to our overall understanding of human physiology and pathophysiology.

Circadian regulation of renal function is particularly important with regards to daily variations in our nutrient and fluid intake. A major function of our kidneys is to maintain homeostasis via the fine-tuned regulation of electrolyte balance and fluid volume. A contributor to the control of fluid balance is the increased release of vasopressin by the brain during the active period compared to the inactive period [7]. Additionally, the expression of vasopressin receptors in the kidneys is controlled by clock genes [8]. Both of these mechanisms work together in order to maintain stable extracellular volume control throughout the day. Contribution of the circadian clock to renal physiology is an active area of investigation. The purpose of this review is to provide a succinct summary of the most recent literature pertaining to the circadian clock in the kidney and speculate on future directions for these important findings. For a more comprehensive summary of this topic, please see [9,10].

Circadian Rhythms Research in the Kidney

Rodents are a useful model when studying circadian rhythms in the kidney due to the similarities in renal function and the daily fluctuations that occur in these functions when compared to humans [10,11]. An important note to consider is that mice and rats are nocturnal, or active during the night, as opposed to humans who are diurnal, or normally active in the day. Consequently, renal functions that exhibit circadian rhythms, such as electrolyte excretion, renal blood flow, filtration, and oxygenation of renal tissue, peak in the night-time when the mice and rats are active instead of the daytime as seen in humans [12]. Although the kidneys are not the only organs that express clock genes, they are second only to the liver in terms of the number of genes that exhibit circadian cycles [13] suggesting that the circadian clock is particularly important to the health and proper function of the kidneys. Indeed, components of the circadian clock have been linked to each tubule segment via *in vitro* cell culture studies or *in vivo* animal experiments focused on transporters associated with specific cell types (**Figure 1**).

Sodium Handling

Per1

The kidneys exhibit circadian rhythms in function including blood pressure control [14], glomerular filtration rate [15], and tubular handling [15,16]. The majority of recent circadian research focuses on sodium balance and its effects on blood pressure. The diurnal rhythm of tubular handling, particularly sodium handling, occurs independent of posture and food/water intake [17]. *Per* genes 1 and 2 have been described as the best candidates for conducting circadian oscillations partly due to their short half-life [18]. The clock gene *Per1* in the kidney is an early aldosterone target gene that transcriptionally regulates targets such as the expression of epithelial sodium channel (ENaC), sodium-glucose linked transporter-1, sodium-hydrogen exchanger-3, and endothelin-1 (ET-1) which are essential in controlling

sodium reabsorption [19–22]. When *Per1* knockout mice are challenged with a relatively mild treatment of high salt (HS) and deoxycorticosterone pivalate (DOCP), which is a long-acting analog of aldosterone, the night/day difference of sodium excretion is attenuated and the blood pressure dip during the inactive period is lost [23,24]. Blood pressure normally dips 10–20% during the inactive period. Individuals who do not exhibit this drop in blood pressure are termed ‘non-dippers’. Along with this non-dipping phenotype, *Per1* knockout mice following HS/DOCP treatment also exhibit dysfunction in the expression of sodium handling genes causing altered sodium excretion [24]. Furthermore, a distal nephron-specific *Per1* knockout mouse was created using cadherin Cre recombinase, which resulted in improper regulation of sodium transporter genes [24]. These studies suggest that *Per1*-dependent transcriptional regulation of Na handling genes is important for the maintenance of 24-hour blood pressure and that this effect is dependent on the actions in the distal nephrons. This model can be used to determine the contribution of non-dipping to changes in kidney function and development of injury.

Bmal1.

Bmal1 stimulates transcription of numerous genes that have been linked to maintaining proper kidney function [25,26]. This relationship has also been shown in kidney-specific knockout mice where *Bmal1* was knocked out specifically in renin-producing cells (Renin1dCre-positive). These mice exhibited decreased urine osmolality and increased urine volume compared to controls [26]. Global *Bmal1* knockout mice lost their circadian rhythm in blood pressure such that their blood pressure did not rise during the active period. This response was associated with a reduction in plasma catecholamines [27]. Spontaneously hypertensive rats (SHR) are another animal model that is often used to study the role of *Bmal1* with blood pressure regulation [28]. In this study, single nucleotide polymorphism (SNP) databases were analyzed to discover that SNPs in the *Bmal1* gene are associated with hypertension in humans [28]. In a recent study, SHR treated with a combination of a calcium channel blocker and an angiotensin receptor blocker to reduce blood pressure also exhibited a reduction in *Bmal1* mRNA levels in the kidneys [29]. Inducible, kidney-specific knockout mice have been studied to determine the role of *Bmal1* specifically in renal nephrons using *Bmal1*lox/lox/Pax8-rtTA/LC1 mice [30]. The metabolome in the plasma of the whole-nephron-specific *Bmal1* knockout mice was altered compared to littermate controls [30]. There was an increase in plasma urea and creatinine levels in the knockouts which was attributed to the decreased renal expression levels of OAT3 [30]. Blood pressure measurements indicated that inducible, nephron-specific *Bmal1* knockout mice exhibit significantly lower systolic blood pressure compared to control. The circadian rhythm of blood pressure in the knockout mice was comparable to controls [30]. *Bmal1* in the adult male mouse kidney thus appears to play a role in blood pressure regulation and renal function; however, its role in mediating the circadian rhythm of blood pressure may be extra-renal. Exploring the mechanisms by which *Bmal1* affects blood pressure may give insight on how SNPs in *Bmal1* could lead to pathophysiology in humans.

Timing Cues; Intrinsic and Extrinsic

Endothelin.

Endothelin-1 (Edn1) is a PER1 target gene [31] which exhibits a circadian expression at the level of mRNA [32]. Gene expression of ETa and ETb receptors in the kidneys changes depending on the time of day. The expression of these genes is not altered in *Per1* heterozygote mice, however, endothelin-1 levels during the active period are higher in inner medullary collecting duct cells isolated from *Per1* heterozygote mice compared to wild type mice on the 129/sv background strain [31]. HS stimulates renal ET-1 production and activation of the ETb receptor [33]. Additionally, HS can alter the circadian rhythm of blood pressure. Therefore, recent studies looked at the role of ET-1 receptors in response to HS. In a comprehensive study, Johnston et al. demonstrated that rats lacking ETb receptor function have an impaired natriuretic response to an acute salt load which depends on the time of day [34]. This response suggests that there is an interaction between endothelin and the circadian clock to regulate the renal excretion of salt. In an additional study, Speed et al. found that *Bmal1* displayed a phase shift of expression in control rats after HS, however, this shift was not present in rats lacking ETb receptors [35] suggesting that ET-1, through ETb, is necessary for normal circadian clock gene expression rhythms. The sodium channels that were affected in this study were not determined; however, cultured inner medullary collecting duct cells treated with ET-1 exhibited a drop in alpha ENaC protein expression [35]. Taken together, these data suggest that ET-1 is both a target of and perhaps a timing cue for the circadian clock.

Vasopressin.

There is a rhythm in vasopressin release which is highest during sleep in order to retain water due to the lack of water intake at this time [36]. A recent study by Hara et al. found that the rat inner medulla, but not the cortex, has a diurnal rhythm in osmotic pressure, where the peak is reached during the active phase and the nadir during the inactive phase [37]. This rhythm was also displayed with sodium, chloride, and urea inner medullary concentrations. These patterns were attributed to matching rhythms in vasopressin receptors V1aR and V2R, aquaporin 2, and the urea transporter UT-A2 occurring in the inner medulla. To beautifully demonstrate the circadian rhythms of clock proteins and localization in the renal medulla, a PER2-Luciferase-2 knock-in mouse was used for macroscopic bioluminescence imaging [37]. The renal medulla regulates urine osmolality by several mechanisms included in this study, which strengthens the importance of the circadian clock on this process. Vasopressin is a critical circulating hormone that is rhythmically released in order to synchronize peripheral clocks.

Corticosteroids.

Cortisol has long been considered a primary synchronizing cue for the peripheral clocks [38]. There is mounting evidence of the contribution of the adrenal glands to the circadian clock in the kidney. A seminal study in 1977 demonstrated that plasma cortisol plays a key role in the circadian rhythm of renal function [39]. Hormones released by the adrenal glands, such as cortisol and aldosterone, have a circadian rhythm [39,40]. The removal of the adrenal glands, eliminating any production of these hormones, lowers the amplitude of

mRNA from renal core clock genes and clock-output genes [41]. Alternatively, chronic administration of corticosterone to healthy mice, maintaining plasma levels midway between the physiological peak and trough, resulted in an increase in *Bmal1* and *Per1* during the inactive phase. This effect was associated with increased phosphorylation of the thiazide-sensitive sodium-chloride cotransporter (NCC) and a 'non-dipping' blood pressure phenotype [42]. Night-time dosing of hydrochlorothiazide treatment in these mice reversed the non-dipping phenotype back to normal, which was attributed to the long half-life of thiazides. Furthermore, adrenalectomy resulted in a blunted rhythm of phosphorylated NCC expression in the kidney [42]. Future studies of this type with other natriuretic or diuretic agents may shed light on additional mechanisms that likely contribute to the normal blood pressure rhythm. Several hormones are key for communication throughout the body with regard to circadian cues. Understanding the role of adrenal hormones may be a crucial link between the central clock in the SCN and peripheral clocks, especially with kidney function.

Renal Nerves.

Although the mechanisms are incompletely understood, nervous system signaling is an important timing cue among the peripheral clocks, which has also been described to be true for the kidneys. Renal nerves stimulate renin secretion and sodium reabsorption directly as well as indirectly by vasoconstriction of afferent and efferent arterioles. A rat model of metabolic syndrome (SHR/NDmcr-cp rats on standard diet) with non-dipping hypertension exhibited a large reduction in blood pressure, along with normalization of the blood pressure circadian rhythm following renal denervation. This was partially attributed to an increase in natriuresis due to suppression of renin production and reduction in NCC overexpression [43]. Although clock genes were not measured, NCC has been associated with some of these genes previously [44] as well as with glucocorticoid signaling and blood pressure rhythms [42]. An additional study also demonstrated that renal denervation partially corrected disruptions in diurnal autonomic tone in ETB-deficient rats [45]. Renal denervation has been tested as a clinical treatment for hypertension with controversial results. Targeting the effects of renal denervation that are beneficial could be considered to provide better outcomes.

Novel Links to the Renal Circadian Clock

Microbiota.

The effect of the microbiota on physiological processes in the body is a field that is quickly growing. A recent report was able to determine the circadian rhythms found in gut bacteria with the entrainment of the clock in peripheral organs, including the kidney [46]. This group concluded that the microbiota modulates the phase of the host peripheral clocks by the release of short-chain fatty acids (SCFA) released from the bacteria, specifically the SCFA lactate [46]. This relationship is intriguing given the extremely diverse microbiota and how the population can change drastically depending on the diet of the host. Promotion of a more beneficial composition of the gut microbiota in mice achieved by a high fiber diet prevented a DOCA induced elevation in blood pressure, circadian pressures were not provided. A similar response occurred following treatment with acetate, which is another SCFA that is released by bacteria. The expression of multiple genes in the kidney were changed following a high fiber diet and acetate supplementation where 244 similar genes were affected in the

same fashion, particularly *Bmal1* which was highly down regulated in both high fiber and acetate treated mice. An additional parameter that was assessed in this study was renal fibrosis. Acetate supplementation prevented fibrosis formation following DOCA treatment; however, it is important to note that a high fiber diet did not attenuate fibrosis. These studies provide evidence that continued research should include full integrative physiology.

Fibrosis.

Other studies have more directly examined the relationship between the clock and renal fibrosis. Circadian genes regulate the expression of genes that are pro-fibrotic such as CTGF, fibronectin, and tumor necrosis factor- α in cell culture [47]. Mice with inducible KO of *BMAL1* in renal tubular cells did not display fibrosis or inflammation in the kidney compared to controls [30]. Furthermore, uninephrectomized *CLOCK*^{-/-} mice, which express a mutant of the *CLOCK* protein that is unable to dimerize with *BMAL1*, had attenuated renal inflammatory responses compared to wild type following HS/DOCP treatment which is mediated by mineralocorticoid receptor signaling [48]. Conversely, *CLOCK*-deficient mice when challenged with unilateral ureteral obstruction had greater fibrosis compared to wild type [49]. Increased oxidative stress and fibrotic tissue assessed by immunohistochemistry and Western were observed following ureter obstruction in *Clock* knockout mice compared to wild type which was mediated by transforming growth factor beta [49]. It is possible that different stimuli result in opposing responses within the same pathway. It should also be noted that the dominant negative-acting *CLOCK*^{-/-} model is distinct from the global *Clock* knockout due to the nature of the mutant *CLOCK* protein but also the background strain of mouse. Additional studies need to be conducted to clarify the role of circadian genes in renal fibrosis.

Sex.

It is well established that men have higher blood pressure than age-matched, premenopausal women [50], stressing the need to include both sexes in studies involving renal and cardiovascular diseases. However, the influence of sex on kidney circadian rhythms is not well studied. In the aforementioned studies that examined the contribution of circadian factors of sodium excretion and blood pressure, only male animals were used. Johnston et al. was an exception since this group included female rats when assessing night:day sodium excretion and blood pressure in control and *ETb* deficient mice. Females were reported to have more efficient natriuresis compared to males [34]. Circadian clock gene and protein levels were not assessed in this study. Sex hormones play a role in renal sodium handling [51], supporting the need to include females in future studies to determine if the circadian clock contributes to the lower blood pressure often observed in premenopausal female rodent models.

Implications of the Kidney Clock for Human Health

Kidney Disease.

It is well reported in the clinical field that renal diseases are associated with the development of sleeping disorders, which are oftentimes treatable by a number of interventions [52]. The cause is difficult to determine, however, due to numerous comorbidities that are present

alongside kidney disease that also likely contribute to altered sleep habits, such as obesity and Type 2 diabetes [53]. Furthermore, some studies associate the lower quality of sleep with worse chronic kidney disease outcomes [54,55]. Conversely, less is known regarding whether abnormal sleeping patterns lead to dysfunction of the kidney. A recent report concludes that a lack of sleep correlated with a more rapid decline in kidney function [56] which supports the theory that a disrupted circadian rhythm is damaging to the kidneys. Sleeping disorders have been linked to the development of diabetes and elevated blood pressure, which can also lead to kidney injury [6,57]. There is a growing field in basic research that is attempting to better understand the role of circadian rhythm in the kidney and its connection to renal pathophysiology.

Chronotherapy.

A potential strategy to improve the efficacy and reduce side effects of medication is chronotherapy, or the administration of medication at certain times of the day. This area is being actively studied in hypertensive patients. A MAPEC study examined this phenomenon among 2000 patients from a single health center, who were monitored after receiving medication either in the morning or evening. The patients who were administered blood pressure medication at night had lower nocturnal pressures and increased dipping compared to day which resulted in a lower risk of cardiovascular disease [58]. The Hygia Project is an ongoing assessment of a much larger population where clinical reports are analyzed from multiple health facilities [59,60]. Additionally, a recent study in rats used hypertensive therapy in the morning and evening and found that treatment before the inactive period was more beneficial for the rats than before the active [29]. However, this was only seen with short-term treatment of 1 week and no difference was seen with long-term treatment [29]. The American Diabetes Association has acknowledged these results and has even suggested administration of antihypertensive drugs in the evening [61]. The effect of chronotherapy on kidney health and function needs to be further examined.

Considerations for Research

The importance of rigor and reproducibility has been at the forefront of research after the publication by Begley and Ellis [62]. This article exposed the inability to reproduce results in a number of landmark studies leading to an emphasis on rigor and reproducibility. Several modalities have been raised to help improve this problem, including a new section to address these areas in NIH grant applications. An overlooked contributor to inconsistent results is the acknowledgement of circadian rhythms [63]. Few studies report the time of day in their methods let alone factor in the time of day when planning experiments. Consequently, data collected without considering the time of day may be difficult to reproduce especially if the collections/measurements in subsequent studies were taken at different times. Furthermore, measurements and collections are normally performed during the daytime, which for rodents is the inactive period when many of the renal physiological processes are in the nadir stage. These issues should be considered in all biomedical research studies.

Conclusion

A growing body of evidence suggests that the molecular circadian clocks located in our cells and tissues are critical to physiological function. The complex interaction between the brain, adrenal glands (hormones), and kidneys likely plays an important part in the regulation of circadian rhythms in renal function. Increasing our understanding of how the central and peripheral clocks work together to regulate physiological processes such as renal function and blood pressure will potentially lead to improved treatments for hypertension and kidney disease.

We wish to confirm that there are no known conflicts of interest associated with this manuscript, “Recent Advances in Understanding the Circadian Clock in Renal Physiology.” There has been no significant financial support for this work that could have influenced its outcome.

References

1. Buijs FN, Leôn-Mercado L, Guzman-Ruiz M, Guerrero-Vargas NN, Romo-Nava F, Buijs RM: The Circadian System: A Regulatory Feedback Network of Periphery and Brain. *Physiology* (Bethesda) 2016, 31:170–181. [PubMed: 27053731]
2. Callaway E, Ledford H: Medicine Nobel awarded for work on circadian clocks. *Nature* 2017, 550:18. [PubMed: 28980662]
3. Partch CL, Green CB, Takahashi JS: Molecular architecture of the mammalian circadian clock. *Trends Cell Biol* 2014, 24:90–99. [PubMed: 23916625]
4. Gumz ML, Rabinowitz L, Wingo CS: An Integrated View of Potassium Homeostasis. *N Engl J Med* 2015, 373:60–72. [PubMed: 26132942]
5. Mocellin S, Tropea S, Benna C, Rossi CR: Circadian pathway genetic variation and cancer risk: evidence from genome-wide association studies. *BMC Med* 2018, 16:20. [PubMed: 29455641]
6. Carter JR, Grimaldi D, Fonkoue IT, Medalie L, Mokhlesi B, Van Cauter E: Assessment of Sympathetic Neural Activity in Chronic Insomnia: Evidence for Elevated Cardiovascular Risk. *Sleep* 2018.
7. Jin X, Shearman LP, Weaver DR, Zylka MJ, de Vries GJ, Reppert SM: A molecular mechanism regulating rhythmic output from the suprachiasmatic circadian clock. *Cell* 1999, 96:57–68. [PubMed: 9989497]
8. Zuber AM, Centeno G, Pradervand S, Nikolaeva S, Maquelin L, Cardinaux L, Bonny O, Firsov D: Molecular clock is involved in predictive circadian adjustment of renal function. *Proc Natl Acad Sci U S A* 2009, 106:16523–16528. [PubMed: 19805330]
9. Douma LG, Gumz ML: Circadian clock-mediated regulation of blood pressure. *Free Radic Biol Med* 2017.
10. Solocinski K, Gumz ML: The Circadian Clock in the Regulation of Renal Rhythms. *J Biol Rhythms* 2015, 30:470–486. [PubMed: 26527094]
11. Johnston JG, Pollock DM: Circadian regulation of renal function. *Free Radic Biol Med* 2018.
12. Emans TW, Janssen BJ, Joles JA, Krediet CTP: Circadian Rhythm in Kidney Tissue Oxygenation in the Rat. *Front Physiol* 2017, 8:205. [PubMed: 28428757]
13. Zhang R, Lahens NF, Ballance HI, Hughes ME, Hogenesch JB: A circadian gene expression atlas in mammals: implications for biology and medicine. *Proc Natl Acad Sci U S A* 2014, 111:16219–16224. [PubMed: 25349387]
14. Salwa P, Gorczyca-Michta I, Kluk M, Dziubek K, Wozakowska-Kapłan B: Variability of circadian blood pressure profile during 24-hour ambulatory blood pressure monitoring in hypertensive patients. *Kardiol Pol* 2014, 72:432–437. [PubMed: 24526553]

15. Koopman MG, Koomen GC, Krediet RT, de Moor EA, Hoek FJ, Arisz L: Circadian rhythm of glomerular filtration rate in normal individuals. *Clin Sci (Lond)* 1989, 77:105–111. [PubMed: 2667855]
16. MILLS JN, STANBURY SW: Persistent 24-hour renal excretory rhythm on a 12- hour cycle of activity. *J Physiol* 1952, 117:22–37. [PubMed: 14946727]
17. BRUN C, KNUDSEN EO, RAASCHOU F: The influence of posture on the kidney function; the fall of the diuresis in the erect posture. *Acta Med Scand* 1945, 122:315–331. [PubMed: 21013575]
18. D'Alessandro M, Beesley S, Kim JK, Chen R, Abich E, Cheng W, Yi P, Takahashi JS, Lee C: A tunable artificial circadian clock in clock-defective mice. *Nat Commun* 2015, 6:8587. [PubMed: 26617050]
19. Stow LR, Richards J, Cheng KY, Lynch IJ, Jeffers LA, Greenlee MM, Cain BD, Wingo CS, Gumz ML: The circadian protein period 1 contributes to blood pressure control and coordinately regulates renal sodium transport genes. *Hypertension* 2012, 59:1151–1156. [PubMed: 22526258]
20. Gumz ML, Stow LR, Lynch IJ, Greenlee MM, Rudin A, Cain BD, Weaver DR, Wingo CS: The circadian clock protein Period 1 regulates expression of the renal epithelial sodium channel in mice. *J Clin Invest* 2009, 119:2423–2434. [PubMed: 19587447]
21. Gumz ML, Popp MP, Wingo CS, Cain BD: Early transcriptional effects of aldosterone in a mouse inner medullary collecting duct cell line. *Am J Physiol Renal Physiol* 2003, 285:F664–673. [PubMed: 12770840]
22. Solocinski K, Richards J, Ali S, Cheng KY, Khundmiri SJ, Gumz ML: Transcriptional regulation of NHE3 and SGLT1 by the circadian clock protein Per1 in proximal tubule cells. *Am J Physiol Renal Physiol* 2015, 309:F933–942. [PubMed: 26377793]
23. Solocinski K, Holzworth M, Wen X, Cheng KY, Lynch IJ, Cain BD, Wingo CS, Gumz ML: Desoxycorticosterone pivalate-salt treatment leads to non-dipping hypertension in Per1 knockout mice. *Acta Physiol (Oxf)* 2017, 220:72–82. [PubMed: 27636900]
- 24*. Douma LG, Holzworth MR, Solocinski K, Masten SH, Miller AH, Cheng KY, Lynch IJ, Cain BD, Wingo CS, Gumz ML: Renal Na Handling Defect Associated with PER1-Dependent Non-Dipping Hypertension In Male Mice. *Am J Physiol Renal Physiol* 2018 This group builds on a previous work to determine the reason of the non-dipping phenotype that occurs in Per1 knockout mice following high salt and desoxycorticosterone treatment. Studies conclude that these mice possess the inability to regulate sodium at the gene level. In doing so, a novel mouse model (distal nephron-specific Per1 knockout) was used to demonstrate a contribution of the WNK, NCC, and ENaC pathway. This article provides insight on a possible cause of non-dipping hypertension.
25. Zhang D, Pollock DM: Circadian regulation of kidney function - finding a role for Bmal1. *Am J Physiol Renal Physiol* 2017.
26. Tokonami N, Mordasini D, Pradervand S, Centeno G, Jouffe C, Maillard M, Bonny O, Gachon F, Gomez RA, Sequeira-Lopez ML, et al.: Local renal circadian clocks control fluid-electrolyte homeostasis and BP. *J Am Soc Nephrol* 2014, 25:1430–1439. [PubMed: 24652800]
27. Curtis AM, Cheng Y, Kapoor S, Reilly D, Price TS, Fitzgerald GA: Circadian variation of blood pressure and the vascular response to asynchronous stress. *Proc Natl Acad Sci U S A* 2007, 104:3450–3455. [PubMed: 17360665]
28. Woon PY, Kaisaki PJ, Bragança J, Bihoreau MT, Levy JC, Farrall M, Gauguier D: Aryl hydrocarbon receptor nuclear translocator-like (BMAL1) is associated with susceptibility to hypertension and type 2 diabetes. *Proc Natl Acad Sci U S A* 2007, 104:14412–14417. [PubMed: 17728404]
29. Potucek P, Radik M, Doka G, Kralova E, Krenek P, Klimas J: mRNA levels of circadian clock components Bmal1 and Per2 alter independently from dosing time-dependent efficacy of combination treatment with valsartan and amlodipine in spontaneously hypertensive rats. *Clin Exp Hypertens* 2017, 39:754–763. [PubMed: 28665713]
- 30*. Nikolaeva S, Ansermet C, Centeno G, Pradervand S, Bize V, Mordasini D, Henry H, Koesters R, Maillard M, Bonny O, et al.: Nephron-Specific Deletion of Circadian Clock Gene Bmal1 Alters the Plasma and Renal Metabolome and Impairs Drug Disposition. *J Am Soc Nephrol* 2016, 27:2997–3004. Nikolaeva et al. examined the role of the Bmal1 gene in metabolic processes in the kidney by using a tubular conditional knockout. A major finding is the dysregulation of drug

excretion in knockout mice. This study demonstrates the importance of Bmal1 in the kidney in metabolic homeostasis throughout the whole body. [PubMed: 27056296]

31. Richards J, Welch AK, Barilovits SJ, All S, Cheng KY, Wingo CS, Cain BD, Gumz ML: Tissue-specific and time-dependent regulation of the endothelin axis by the circadian clock protein Per1. *Life Sci* 2014, 118:255–262. [PubMed: 24721511]
32. Pizarro A, Hayer K, Lahens NF, Hogenesch JB: CircaDB: a database of mammalian circadian gene expression profiles. *Nucleic Acids Res* 2013, 41:D1009–1013. [PubMed: 23180795]
33. Jin C, Speed JS, Pollock DM: High salt intake increases endothelin B receptor function in the renal medulla of rats. *Life Sci* 2016, 159:144–147. [PubMed: 26724217]
- 34*. Johnston JG, Speed JS, Jin C, Pollock DM: Loss of endothelin B receptor function impairs sodium excretion in a time- and sex-dependent manner. *Am J Physiol Renal Physiol* 2016, 311 :F991–F998. These authors used a novel experimental design to consider both sex and time-of-day as key variables in a study to examine the role of Endothelin-1 in the excretion of an acute salt load. Johnston et al. found that a salt load administered at the start of the active period was better excreted than that given at the start of the rest period. These findings have important implications for humans in terms of understanding the risks associated with eating salty foods late at night. [PubMed: 27582096]
- 35*. Speed JS, Hyndman KA, Roth K, Heimlich JB, Kasztan M, Fox BM, Johnston JG, Becker bK, Jin C, Gamble KL, et al.: High dietary sodium causes dysynchrony of the renal molecular clock in rats. *Am J Physiol Renal Physiol* 2018, 314:F89–F98. Speed and colleagues performed a large scale study in order to assess the effect of a high sodium diet on circadian clock gene expression in the rat kidney. High salt diet caused changes in rhythmic expression of the Bmal1 gene in the renal inner medulla but not the cortex, and this effect appeared to be mediated via the Endothelin-B receptor. These findings have important implications for understanding the effect of dietary salt on the molecular machinery of the circadian clock in the kidney. [PubMed: 28971988]
36. Trudel E, Bourque CW: Central clock excites vasopressin neurons by waking osmosensory afferents during late sleep. *Nat Neurosci* 2010, 13:467–474. [PubMed: 20190744]
37. Hara M, Minami Y, Ohashi M, Tsuchiya Y, Kusaba T, Tamagaki K, Koike N, Umemura Y, Inokawa H, Yagita K: Robust circadian clock oscillation and osmotic rhythms in inner medulla reflecting cortico-medullary osmotic gradient rhythm in rodent kidney. *Sci Rep* 2017, 7:7306. [PubMed: 28779094]
38. Balsalobre A, Brown SA, Marcacci L, Tronche F, Kellendonk C, Reichardt HM, Schütz G, Schibler U: Resetting of circadian time in peripheral tissues by glucocorticoid signaling. *Science* 2000, 289:2344–2347. [PubMed: 11009419]
39. Moore-ede MC, Schmelzer WS, Kass DA, Herd JA: Cortisol-mediated synchronizaton of circadian rhythm in urinary potassium excretion. *Am J Physiol* 1977, 233:R230–238. [PubMed: 411380]
40. Leliavski A, Dumbell R, Ott V, Oster H: Adrenal clocks and the role of adrenal hormones in the regulation of circadian physiology. *J Biol Rhythms* 2015, 30:20–34. [PubMed: 25367898]
41. Soték M, Bryndová J, Ergang P, Vagnerová K, Kvapilová P, Vodicka M, Pécha J, Sumová A: Peripheral circadian clocks are diversely affected by adrenalectomy. *Chronobiol Int* 2016, 33:520–529. [PubMed: 27031999]
- 42*. Ivy JR, Oosthuyzen W, Peltz TS, Howarth AR, Hunter RW, Dhaun N, Al-Dujaili EA, Webb DJ, Dear JW, Flatman PW, et al.: Glucocorticoids Induce Nondipping Blood Pressure by Activating the Thiazide-Sensitive Cotransporter. *Hypertension* 2016, 67:1029–1037. These authors demonstrated a role for the renal distal convoluted tubule sodium chloride co-transporter NCC in the maintenance of normal 24 hour blood pressure rhythms in the setting of disrupted corticosterone rhythms. This article provides the first evidence that the active, phosphorylated form of NCC is higher during the mouse active period compared to the rest period which has important implications for optimizing the timing of thiazide administration. [PubMed: 26953322]
43. Katayama T, Sueta D, Kataoka K, Hasegawa Y, Koibuchi N, Toyama K, Uekawa K, Mingjie M, Nakagawa T, Maeda M, et al.: Long-term renal denervation normalizes disrupted blood pressure circadian rhythm and ameliorates cardiovascular injury in a rat model of metabolic syndrome. *J Am Heart Assoc* 2013, 2:e000197. [PubMed: 23974905]
44. Richards J, Ko B, All S, Cheng KY, Hoover RS, Gumz ML: A role for the circadian clock protein Per1 in the regulation of the NaCl co-transporter (NCC) and the with-no-lysine kinase (WNK)

cascade in mouse distal convoluted tubule cells. *J Biol Chem* 2014, 289:11791–11806. [PubMed: 24610784]

45. Becker BK, Feagans AC, Chen D, Kasztan M, Jin C, Speed JS, Pollock JS, Pollock DM: Renal denervation attenuates hypertension but not salt sensitivity in ET. *Am J Physiol Regul Integr Comp Physiol* 2017, 313:R425–R437. [PubMed: 28701323]
46. Tahara Y, Yamazaki M, Sukigara H, Motohashi H, Sasaki H, Miyakawa H, Haraguchi A, Ikeda Y, Fukuda S, Shibata S: Gut Microbiota-Derived Short Chain Fatty Acids Induce Circadian Clock Entrainment in Mouse Peripheral Tissue. *Sci Rep* 2018, 8:1395. [PubMed: 29362450]
47. Petržilka S, Taraborrelli C, Cavadini G, Fontana A, Birchler T: Clock gene modulation by TNF- α depends on calcium and p38 MAP kinase signaling. *J Biol Rhythms* 2009, 24:283–294. [PubMed: 19625730]
48. Fletcher EK, Morgan J, Kennaway DR, Bienvenu LA, Rickard AJ, Delbridge LMD, Fuller PJ, Clyne CD, Young MJ: Deoxycorticosterone/Salt-Mediated Cardiac Inflammation and Fibrosis Are Dependent on Functional CLOCK Signaling in Male Mice. *Endocrinology* 2017, 158:2906–2917. [PubMed: 28911177]
49. Chen WD, Yeh JK, Peng MT, Shie SS, Lin SL, Yang CH, Chen TH, Hung KC, Wang CC, Hsieh IC, et al.: Circadian CLOCK Mediates Activation of Transforming Growth Factor- β Signaling and Renal Fibrosis through Cyclooxygenase 2. *Am J Pathol* 2015, 185:3152–3163. [PubMed: 26458764]
50. Reckelhoff JF: Gender differences in the regulation of blood pressure. *Hypertension* 2001, 37:1199–1208. [PubMed: 11358929]
51. Veiras LC, Girardi ACC, Curry J, Pei L, Ralph DL, Tran A, Castelo-Branco RC, Pastor-Soler N, Arranz CT, Yu ASL, et al.: Sexual Dimorphic Pattern of Renal Transporters and Electrolyte Homeostasis. *J Am Soc Nephrol* 2017, 28:3504–3517. [PubMed: 28774999]
52. Maung SC, El Sara A, Chapman C, Cohen D, Cukor D: Sleep disorders and chronic kidney disease. *World J Nephrol* 2016, 5:224–232. [PubMed: 27152260]
53. Thompson S, James M, Wiebe N, Hemmelgarn B, Manns B, Klarenbach S, Tonelli M, Network AKD: Cause of Death in Patients with Reduced Kidney Function. *J Am Soc Nephrol* 2015, 26:2504–2511. [PubMed: 25733525]
54. Kim CW, Chang Y, Sung E, Yun KE, Jung HS, Ko BJ, Kwon MJ, Hyun YY, Lee KB, Kim H, et al.: Sleep duration and quality in relation to chronic kidney disease and glomerular hyperfiltration in healthy men and women. *PLoS One* 2017, 12:e0175298. [PubMed: 28423054]
55. Li J, Huang Z, Hou J, Sawyer AM, Wu Z, Cai J, Curhan G, Wu S, Gao X: Sleep and CKD in Chinese Adults: A Cross-Sectional Study. *Clin J Am Soc Nephrol* 2017, 12:885–892. [PubMed: 28389618]
56. McMullan CJ, Curhan GC, Forman JP: Association of short sleep duration and rapid decline in renal function. *Kidney Int* 2016, 89:1324–1330. [PubMed: 27165820]
57. Vetter C, Dashti HS, Lane JM, Anderson SG, Schernhammer ES, Rutter MK, Saxena R, Scheer FAJL: Night Shift Work, Genetic Risk, and Type 2 Diabetes in the UK Biobank. *Diabetes Care* 2018, 41:762–769. [PubMed: 29440150]
58. Hermida RC, Ayala DE, Mojón A, Fernandez JR: Influence of circadian time of hypertension treatment on cardiovascular risk: results of the MAPEC study. *Chronobiol Int* 2010, 27:1629–1651.
59. Hermida RC: Sleep-time ambulatory blood pressure as a prognostic marker of vascular and other risks and therapeutic target for prevention by hypertension chronotherapy: Rationale and design of the Hygia Project. *Chronobiol Int* 2016, 33:906–936. [PubMed: 27221952]
60. Hermida RC, Ayala DE, Fernandez JR, Mojón A, Crespo JJ, Ríos MT, Smolensky MH: Bedtime Blood Pressure Chronotherapy Significantly Improves Hypertension Management. *Heart Fail Clin* 2017, 13:759–773. [PubMed: 28865783]
61. de Boer IH, Bangalore S, Benetos A, Davis AM, Michos ED, Muntner P, Rossing P, Zoungas S, Bakris G: Diabetes and Hypertension: A Position Statement by the American Diabetes Association. *Diabetes Care* 2017, 40:1273–1284. [PubMed: 28830958]
62. Begley CG, Ellis LM: Drug development: Raise standards for preclinical cancer research. *Nature* 2012, 483:531–533. [PubMed: 22460880]

63. Gumz ML: Taking into account circadian rhythm when conducting experiments on animals. *Am J Physiol Renal Physiol* 2016, 310:F454–455. [PubMed: 26719365]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HIGHLIGHTS

- Regulation of renal function is influenced by the circadian clock.
- Dysregulation of the molecular clock has been linked to worsened kidney disease and hypertension in rodent models.
- Changes in renal function depending on the time of day should be considered when planning and conducting experiments in rodent models.

Figure 1. Summary of Recent Evidence Linking the Circadian Clock to Renal Function.

Diagram of a nephron indicating the section of the tubules of recent focus as determined by the transporters that were examined in *in vitro* or *in vivo* studies in the last four years. For a more comprehensive review of this topic, see [9,10].