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Review

Autonomic nerves and circadian control of renal function

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ABSTRACT

Cardiovascular and renal physiology follow strong circadian rhythms. For instance, renal excretion of solutes and water is higher during the active period compared to the inactive period, and blood pressure peaks early in the beginning of the active period of both diurnal and nocturnal animals. The control of these rhythms is largely dependent on the expression of clock genes both in the central nervous system and within peripheral organs themselves. Although it is understood that the central and peripheral clocks interact and communicate, few studies have explored the specific mechanism by which various organ systems within the body are coordinated to control physiological processes. The renal sympathetic nervous innervation has long been known to have profound effects on renal function, and because the sympathetic nervous system follows strong circadian rhythms, it is likely that autonomic control of the kidney plays an integral role in modulating renal circadian function. This review highlights studies that provide insight into this interaction, discusses areas lacking clarity, and suggests the potential for future work to explore the role of renal autonomics in areas such as blood pressure control and chronic kidney disease.

1. Introduction: circadian physiology and circadian renal function

Many aspects of human physiology follow strict circadian rhythms (Solocinski and Gumz, 2015). Recent research progress in the field of circadian biology has allowed us to acknowledge the existence of a molecular clock in kidney cells and comprehend how this system works. Most kidney-related functions, if not all, follow a circadian pattern (Nikolaeva et al., 2016) that appear to be under precise control of both central and peripheral circadian clocks that can be affected by all kinds of external factors; e.g., light and dietary salt content (Zhang and Pollock, 2018). Recent evidence suggests that core clock genes regulate essential renal functions along the nephron. Most of this work has focused on their interaction with the renin angiotensin aldosterone system as well as sodium transporters within different segments of the renal tubule (Johnston and Pollock, 2018). Global genetic deletion of core circadian genes in rodents leads to loss of diurnal control of Na^+ and water homeostasis and distinct blood pressure phenotypes (Gumz et al., 2009; Tokonami et al., 2014; Nikolaeva et al., 2016). However, it is worth noting that a majority of circadian gene knockout studies have been conducted in mouse models and may not fully translate to other species, particularly in relation to autonomic control of renal function. Future work is greatly needed to explore the influence of circadian genes both in the central and peripheral (renal) clocks in autonomic control of blood pressure in animals other than mice.

Blood pressure exhibits a 24-hour rhythm in healthy individuals, with two characteristic daytime peaks followed by a 10–20% decrease during sleep (Staessen et al., 1997; Douma and Gumz, 2018). The mechanism(s) for circadian regulation of blood pressure control is not fully understood; however, it is currently accepted that blood pressure circadian rhythm is at least partly determined by clock genes (Johnston and Pollock, 2018). The blood pressure pattern during nighttime, or the inactive period, can be organized into several categories based on its comparison to daytime pressure (Kario, 2018). A "dipper" can be defined as blood pressure lowering at night > 10% of the daytime pressure and is considered characteristic of a normal, healthy blood pressure pattern. An "extreme dipper" is a drop in nighttime pressure of > 20%. A "non-dipper" is generally defined as nighttime blood pressure dropping < 10% of the daytime pressure. A more extreme phenotype is what is referred to as a "riser" or "reverse dipper" where blood pressure is higher at night compared to day. It is important to distinguish that "nocturnal hypertension" includes non-dippers, but is not considered a circadian definition, but rather, a blood pressure higher than a normal range of nighttime blood pressure.

Many conditions and risk factors are associated with a higher nocturnal blood pressure pattern. Several studies have suggested that nocturnal hypertension is caused in part by increased salt-sensitivity as

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well as impaired renal excretory function and is exacerbated by risk factors such as high salt intake, aging, sleep disorders, stress, obesity, and diabetes mellitus. (Thomas et al., 2017; Hermida et al., 2018). A growing number of studies suggest that nighttime blood pressure is an independent predictor for the progression of cardiovascular disease, and should therefore be a major target in the treatment of hypertension (Rahman et al., 2013; Flack et al., 2018). According to the recent American College of Cardiology/American Heart Association hypertension guidelines, nighttime blood pressure should be controlled to ≤110/65 mm Hg (Whelton et al., 2018b).

Because the kidneys express core circadian clock genes (Gumz et al., 2009, 2010; Richards et al., 2012; Tokonami et al., 2014; Nikolaeva et al., 2016), which are influenced by dietary factors such as salt intake (Speed et al., 2018), and because the autonomic nervous also modulates diurnal blood pressure rhythms (Grassi et al., 2010) and renal functions such as solute handling (Johns et al., 2011), it is likely that autonomic control of renal function plays an important role in circadian variability. This review highlights the existing literature exploring the role of the autonomic nervous system in modulating circadian renal function and identifies areas in need of clarification by future studies.

2. Autonomic control and renal function

The kidneys are extensively innervated by sympathetic efferents that affect transport functions along the nephron, vascular tone of afferent and efferent arterioles, and renin release by juxtaglomerular apparatus. In addition, afferent nerves located primarily along the renal pelvis function in a sensory fashion. Efferent sympathetic nerve activity in general results in renin secretion, reabsorption of sodium, and decreases in renal blood flow. These pathways have been extensively reviewed by others (Johns et al., 2011; Grassi et al., 2015; Wehrwein et al., 2016); however, it is worth noting that the vast majority of studies conducted to elucidate the influence of sympathetic activity upon renal function were not designed to investigate the contribution of circadian factors. Thus, further contributions to the body of literature describing the role of autonomic control on renal function that include a circadian perspective are required.

3. Renal nerves and circadian control

Although the importance of the sympathetic nervous system in the maintenance of diurnal blood pressure rhythms is relatively well-established (Diedrich et al., 2003; Kalsbeek et al., 2006; Grassi et al., 2010; Gamble et al., 2014), the role of the renal autonomic nerves in controlling diurnal blood pressure rhythms is less clear. Relatively few studies have reported diurnal rhythms following renal denervation in experimental models and human subjects. Studies from our laboratory have investigated a salt-sensitive rat model of endothelin B receptor deficiency (ETB-def) that demonstrates altered rhythms in blood pressure and heart rate variability following high salt diet (Becker et al., 2017). These effects include significantly greater amplitude in 24-h mean arterial pressure during high salt that is exaggerated in the ETB-def rats (Fig. 1). However, the amplitude of circadian alterations were unaffected by total renal denervation in both ETB-def and transgenic controls. Day/night rhythms in renal excretory function were also unaffected by total denervation in both the ETB-def and transgenic control lines. Other studies demonstrated similarly that renal denervation had no effect on the timing of diurnal blood pressure rhythms in the deoxycorticosterone + high salt rat model of hypertension although both selective afferent denervation and total denervation reduced the amplitude of the day/night difference in blood pressure (Banek et al., 2016). These studies suggest that although the renal nerves may not influence the timing of blood pressure or global sympathetic rhythms, they may contribute to diurnal amplitudes of blood pressure and sympathetic tone and may be influential in dipping status. Further supporting this is a rat model of hypertension with metabolic syndrome, the SHRcp rat, which has a blunted day-night blood pressure rhythm. Renal denervation in this model significantly increased sodium excretion, lowered blood pressure, and also restored a normal, dipper-type diurnal blood pressure rhythm (Katayama et al., 2013).

Renal denervation applied to human patients thus far has had a challenging history. After a number of promising clinical trials, the failure of Simplicity-3 (clinical trial) cast the utility of renal denervation for resistant hypertensive patients into question (Bhatt et al., 2014). A number of potential explanations have been offered for the failure of Simplicity-3, including operator and center inexperience resulting in incomplete denervation (Tzafriri et al., 2014) along with the inclusion of potentially non-resistant hypertensive patients resulting in a Hawthorne effect (Bakris et al., 2014; McCambridge et al., 2014). However, the positive outcomes of SPYRAL HTN-OFF MED and the follow-up study, SPYRAL HTN-ON MED, have reignited and rejuvenated the field of renal denervation in patients (Townsend et al., 2017; Kandzari et al., 2018). This large cohort, clinical trials often employ use of 24-h ambulatory blood pressure monitoring as a primary end-point; however, the data are rarely reported as hourly or night/day values. Importantly, SPYRAL HTN-ON MED reported hourly and night/day blood pressure values following denervation or sham procedure and found that much of the improved blood pressure observed in the denervated subjects occurred during the nighttime hours (Kandzari et al., 2018). Further, in-depth, analysis of this ambulatory blood pressure data will be instrumental in evaluating the contribution of renal sympathetic nerves to diurnal blood pressure phenotypes in hypertensive populations.

In a small cohort of renal denervated patients, half of which presented with a non-dipping blood pressure phenotype before denervation, there was a significant improvement in dipping pattern following denervation (Krum et al., 2009). Another small Irish cohort subjected to bilateral renal denervation via Symplicity catheters also had a significant improvement in dipping status post denervation relative to baseline (Tuohy et al., 2016). These smaller cohort studies lacked a sham control and the dipping status of ambulatory blood pressure data following renal denervation needs to be further characterized in larger clinical cohorts.

Additional evidence that renal nerves may contribute to diurnal blood pressure rhythms comes from a study conducted by Gosse et al. (2017). They found that in patients from the DENERHTN (Renal Denervation for Hypertension) trial, baseline (prior to denervation) nighttime systolic blood pressure and standard deviation of nighttime systolic blood pressure were predictive of a patient's response to renal denervation. The authors speculate that this could be due to nighttime blood pressures being more indicative of a patient's true blood pressure load as it is less influenced by environmental factors or because nighttime blood pressure may be more closely associated with sympathetic tone, such as has been well documented in patients with sleep apnea (Somers et al., 1995; Elmasry et al., 2002; Abboud and Kumar, 2014). In another smaller cohort study, neither renal denervation nor treatment with spironolactone affected day to night blood pressure rhythms; however, renal denervation reduced blood pressure variability more than spironolactone treatment (de la Sierra et al., 2017). These studies indicating a role for renal nerves affecting global blood pressure variability may suggest a potential role for the renal afferent nerves, which are discussed later in this review.

A very large gap exists in our knowledge regarding diurnal rhythms of renal sympathetic tone, especially in disease settings. Much of our understanding of renal sympathetic tone is due to studies conducted on rodents and lagomorphs such as rats and rabbits. These experiments are by and large conducted in acute settings during normal working hours, which correspond with the animals' inactive and sleeping periods. We are very likely missing key time periods through the day where differences in renal sympathetic tone are most important. The laboratory of Geoffry Head has evaluated renal sympathetic tone in rabbits over the course of 24 h and found that RSNA tends to follow a similar rhythm with activity, particularly peaking in the evening hours around dusk,

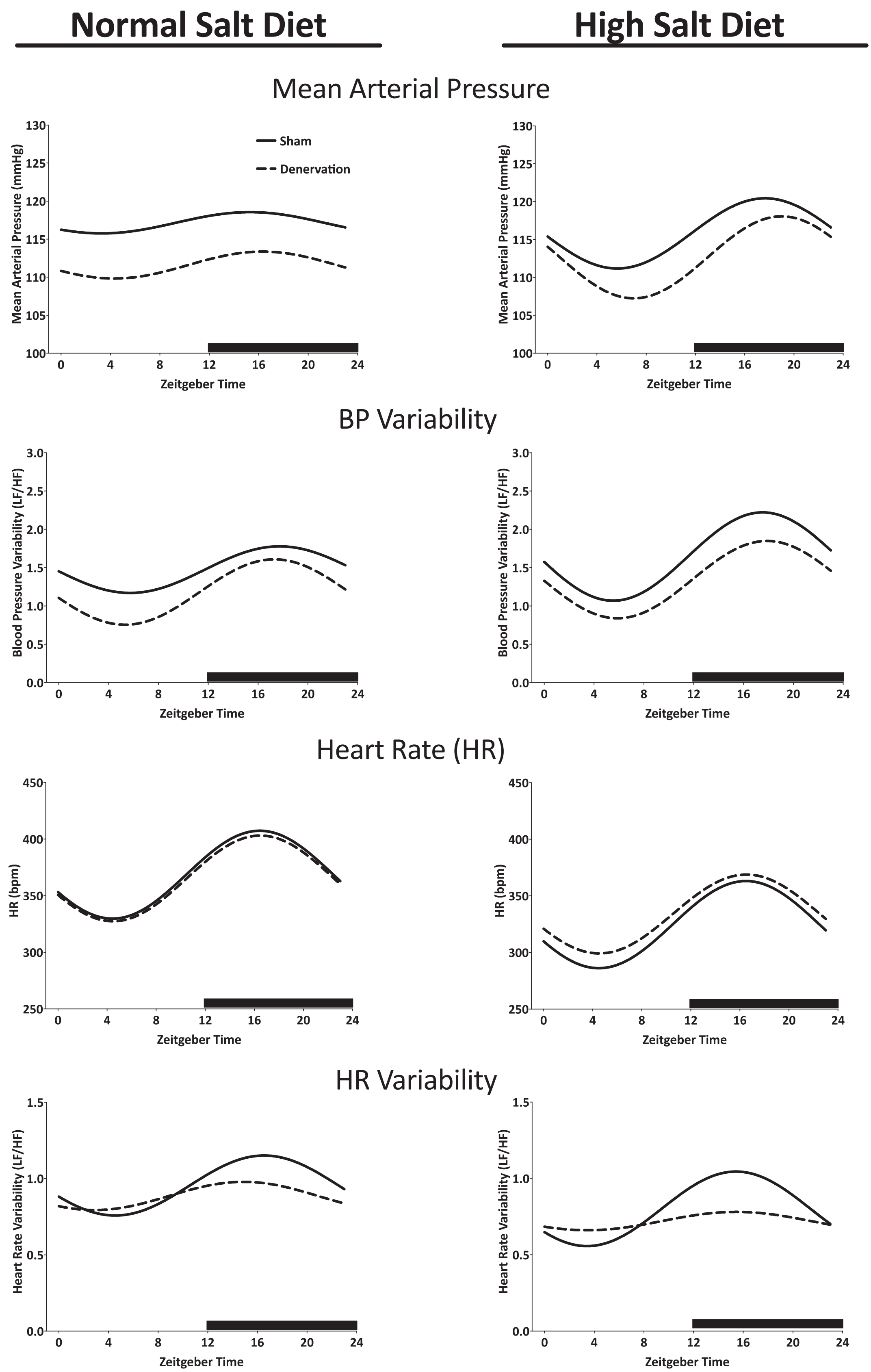

Fig. 1. Typical circadian patterns of mean arterial pressure (MAP) and heart rate (HR) along with frequency analysis of systolic blood pressure (BP) and heart rate variability as determined in conscious control rats using telemetry. Bi-lateral renal denervation had no significant effect on the MAP or BP variability mesor in rats on a normal or high salt diet. However, the amplitude of both MAP and BP variability was significantly increased by high salt diet in both intact and denervated rats. HR was not affected by diet or denervation. The mesor of HR variability appeared to be reduced, but this reduction was not statistically significant. However, there was a small, but significant reduction in the circadian phase of HR variability by about 1–2 h in the denervated rats on either diet.
Adapted from Becker et al., 2017.

which corresponds to the activity pattern of rabbits (Lim et al., 2012). The use of telemeter-based measurements of renal sympathetic tone (Stocker and Muntzel, 2013) will be of great value to future studies investigating these systems; however, the current technical challenges in establishing long-lasting chronic renal nerve recordings limits its utility. Highly skilled and motivated investigators undertaking these challenges will undoubtedly uncover important discoveries in this field.

Another challenge in the field of autonomic control of renal function is the evaluation of species differences. As studies in rodents comprise the large majority of the contribution to the literature in this topic, it is unclear how translatable these findings are to larger mammals or bipedal species such as humans. Other sympathetic nerves have been shown to have differential effects between bipedal and quadrupedal species (Heistad et al., 1978), and others have demonstrated a number of similarities (Charkoudian et al., 2010). Because there is currently no method to directly measure human renal nerve activity outside of invasive surgery, it is currently unknown how human renal sympathetic nerve activity compares to that of experimental animals, especially in a circadian setting. Future work utilizing technological approaches as recently reviewed by Hart et al. (2017) will greatly aid our understanding of species differences in a number of sympathetic pathways.

3.1. Afferent nerves

Another unknown area of study in renal circadian autonomic physiology involves the renal afferents. These communicate sensory information from the kidney to the central nervous system (Stella and Zanchetti, 1991) and facilitate reflexive control of efferent sympathetic tone. In general, physiological stimuli such as high salt diet and endothelin activation of mechanosensory nerves in the renal pelvis promote reflexive inhibition of efferent sympathetic nerve activity (Kopp et al., 2006, 2007, 2009, 2010; Kopp, 2011). Stimulation of afferent nerves by noxious stimuli such as adenosine as in renal ischemia promotes increases in efferent sympathetic tone (Katholi et al., 1985; Converse et al., 1992; Hausberg, 2002). There is currently no information in the literature regarding the diurnal variability of these responses.

Although light is the predominant Zeitgeber, or “time giver,” that synchronizes circadian rhythms, other Zeitgebers such as food intake can influence circadian rhythms. Because the renal afferent reflexes possess exquisite sensitivity to salt, it is likely that the timing of salt intake may have dramatic effects on the sensory pathways of the kidney that would ultimately have numerous physiological consequences to the rest of the body. These are important and currently lacking areas of research that may have profound impact on human health in light of the large quantities of salt currently consumed in the world.

3.2. Chronic kidney disease and nerves

Roughly 60% of chronic kidney disease (CKD) patients have hypertension (Centers for Disease Control and Prevention, 2014), which rises to about 90% in stage 4 of the disease (Horowitz et al., 2015), compared to 32% in the general population (Whelton et al., 2018a). Initial studies established a relationship between chronic kidney disease and high systemic and renal sympathetic activity. Converse et al. (1992) showed that hemodialysis patients (78% were hypertensive) had significantly higher muscle sympathetic nerve discharge compared to nephrectomy patients on dialysis or normal subjects, thus providing an association between chronic kidney disease and increased sympathetic activity. Veiga et al. (2017) reported that renal denervation restored mean arterial pressure (MAP) to normal values in a 5/6 nephrectomy induced CKD in male Wistar rats. Plasma creatinine levels were also significantly improved despite the loss of renal mass suggesting increased GFR and thus a vasodilator effect of denervation. Failure of renal functional improvement in the Converse study may be attributed to the late stage of kidney disease of the subjects, but this needs to be evaluated further.

Renal denervation in a swine model of chronic renal insufficiency produced by ischemia failed to attenuate overall kidney damage as assessed by histology, serum urea, and creatinine, but did result in a decrease in circulating aldosterone in the denervated group (Lubanda et al., 2017) highlighting the involvement of the sympathetic nerves in the renin-aldosterone-angiotensin system in this model. However, there was more damage in the renal artery wall of the denervated group in comparison to the control group, which may complicate interpretation of the results. More studies are needed to examine the mechanisms through which kidney injury contributes to increased sympathetic activity. Specifically, the potential role of the molecular clock has not been evaluated in terms of renal sympathetic nerve function despite clear evidence for circadian control of renal function.

There appears to be a strong link between CKD and alterations to diurnal blood pressure rhythms. Patients with CKD have been demonstrated to have higher incidence of nocturnal hypertension, non-dipping, and altered peak timing of blood pressure rhythms (Portaluppi et al., 1990, 1991; Farmer et al., 1997; Agarwal et al., 2009; Mizuno et al., 2012; Mojon et al., 2013). Dhaun et al. (2014) recently provided evidence that blood pressure lowering in CKD may be able to restore diurnal variations in blood pressure. In a small group of CKD patients whose blood pressures were similar between night and day, addition of an endothelin A receptor selective antagonist (sitaxentan), resulted in a significant drop in nocturnal blood pressure. Whether dysfunction in autonomic tone contributes to the altered diurnal blood pressure rhythm in CKD is uncertain. In a pilot study evaluating the safety and effectiveness of renal denervation in CKD patients, renal denervation was observed to increase the dipping status of CKD patients (Hering et al., 2012). This suggests a potential role for the renal nerves in mediating many of the altered circadian blood pressure phenotypes in CKD patients but needs to be investigated more specifically. Given the likely contribution of afferent nerves in blood pressure control and global autonomic tone, these reflexes will be of particular interest in future work investigating these mechanisms in CKD.

4. Chronotherapy

Chronotherapy offers treatments in which individuals' circadian rhythms can be taken into consideration, and it was acknowledged in the 1970s that timing of medication delivery may play a role in treating hypertensive patients (Bartter et al., 1976). During the past decade, Hermida and colleagues found that bedtime hypertension chronotherapy provides a more beneficial clinical outcome compared to regular daytime delivery of medication (Hermida et al., 2011, 2016, 2018). In the MAPEC (Monitorizaci on Ambulatoria para Pre-dicci on de Eventos Cardiovasculares) study, 3374 normotensive and hypertensive individuals were included and followed for 5.6 years with a primary study endpoint of cardiovascular events. Hypertensive participants were required to take all of their prescribed medication at morning time or take ≥1 of them at bedtime. Results from this study suggested that nighttime blood pressure is an independent indicator for the prognosis of cardiovascular disease and that chronotherapy provides a more effective blood pressure control in individuals that present non-dipping blood pressure pattern. In addition, favorable outcomes were also presented in patients with CKD or uncontrolled HTN by reducing nighttime blood pressure via chronotherapy (Hermida et al., 2014). One limitation of this study is that the class of antihypertensive medications was not properly controlled and it was later suggested that not all prescribed medications exert the same effective blood pressure control when given at bedtime (Acelajado et al., 2012; de la Sierra et al., 2014). A number of studies with smaller sample sizes focused on class of medications which target renal autonomic system, including angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-II receptor blockers (ARB). Witte et al. showed that bedtime administration of Enalapril exerted preferable nighttime blood pressure decline

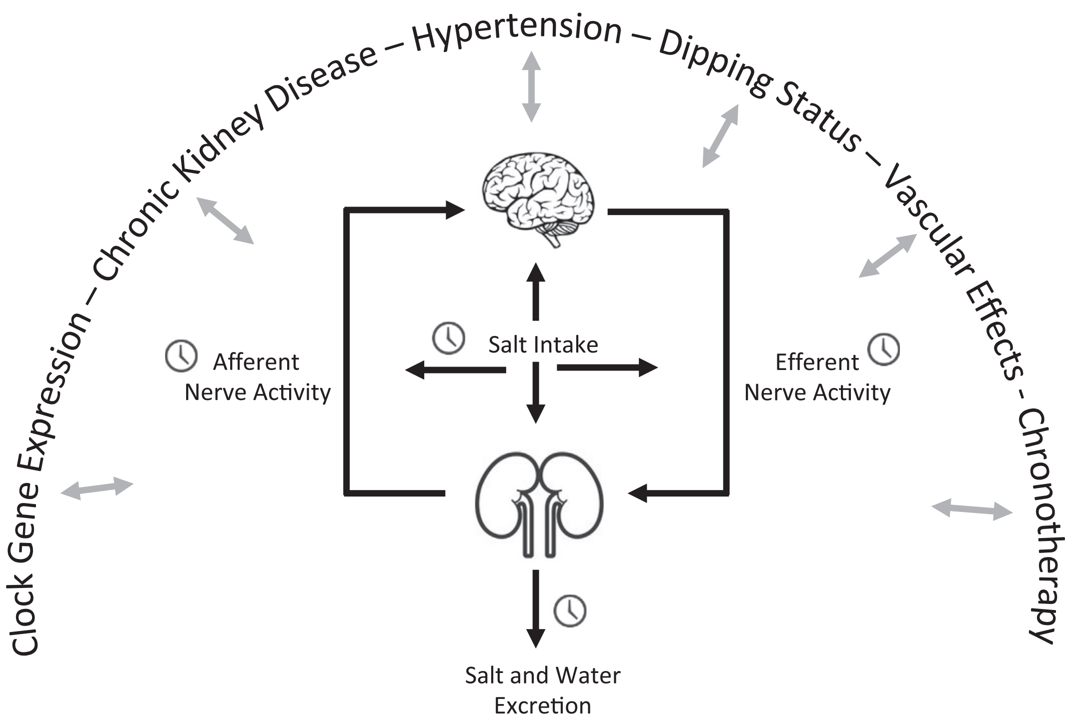

Fig. 2. Hypothetical scheme depicting the interaction of autonomic control of kidney function and the potential impact of factors related to the circadian clock.

compared to morning administration (Witte et al., 1993). Lisinopril also evinced a significantly greater nighttime blood pressure decrease when giving at evening hours (Macchiarulo et al., 1999). In addition, there is some evidence that bedtime administration of Olmesartan and Irbesartan resultes in greater blood pressure decline at night (Tofe Povedano and Garcia De La Villa, 2009). However, a prospective, randomized study carried out at the University of Alabama at Birmingham showed a similar reduction in 24-hour blood pressure when patients were given 3-week treatment of a 3rd generation of beta blocker, Nebivolol, dosed either in the morning or at bedtime. However, it was noted that bedtime dosing of Nebivolol resulted in a reduction in prewaking blood pressure, which might confer a decreased risk of cardiovascular events in the early morning hours (Acelajado et al., 2012). Asmar et al. (2011) examined the effects of morning versus evening dosing of amlodipine combined with valsartan in patients that were not successfully controlled by calcium blocker alone and they showed similar effects on daytime and nighttime blood pressure between morning and evening dosing. In addition to the classes of medications, it was also suggested that antihypertensive chronotherapy exerts distinct effects in different populations. The Rahman et al. (2013) study was designed to determine the effects of morning versus bedtime dosing of antihypertensive medications on nocturnal blood pressure in African Americans with CKD. Results from this study showed that bedtime dosing did not lead to significant reductions in either nocturnal or 24-hour blood pressure. It is apparent that more trials are needed to determine the timing effect in different classes of antihypertensive medications as well as different combination regimens, in larger populations.

Interestingly, alterations in the timing of food intake have been shown to contribute to the regulation of blood pressure. Mochel et al. (2014) performed a study where they examined the response to different feeding schedules. Dogs were fed the same diet at either 7 am, 1 pm or 7 pm. Blood pressure followed a circadian rhythm when dogs were fed at 7 am. Surprisingly, the 6- or 12-hour delay of food intake caused a shift of the circadian rhythm of blood pressure. In a more recent study, Cote et al. (2018) investigated the effect of time restricted feeding in blood pressure regulation in the setting of obesity. They found that high fat diet increased blood pressure in rats; however, introduction of 3-week active phase feeding led to a 17 mm Hg decrease in arterial pressure. The mechanism(s) by which time of food intake affects blood pressure level and rhythm is not fully understood; however, there is some evidence that dietary salt content may play a pivotal role in circadian blood pressure regulation. A study was carried out in a group of 42 hypertensive participants, 21 of which were classified as salt sensitive whereas the remaining 21 patients were considered salt resistant. Participants were on a high salt diet for one week followed by another week on a low sodium diet. The decline in nocturnal blood pressure was significantly diminished in salt-sensitive participants compared to that of non-salt-sensitive participants. Interestingly, one-week salt restriction restored the blood pressure pattern from non-dipping to dipping, suggesting that salt content may play a role in blood pressure regulation (Uzu et al., 1997).

5. Sex differences

The notion that biological sex contributes to differences in autonomic control of blood pressure has been well established and extensively reviewed elsewhere (Hart and Charkoudian, 2014; Baker et al., 2016; Joyner et al., 2016). These studies mostly address global sympathetic tone and vascular function; therefore, there remains a large gap in the literature regarding the role of biological sex on autonomic control of renal function and a particular absence of studies specifically investigating these factors in a circadian setting. In the Lewis Polycystic Kidney rat model of CKD, reflexive renal sympathoinhibition following vagal nerve stimulation was blunted in females but not males (Salman et al., 2017). Work by the Barrett group has demonstrated that biological sex influences baroreflex control of renal sympathetic nerve activity following myocardial infarction (Pinkham et al., 2015), and that female rats have attenuated renal sympathetic nerve activation in the minutes following myocardial infarction relative to males (Pinkham et al., 2012). These studies, along with the known contribution of biological sex towards autonomic control of blood pressure warrant further investigation into circadian autonomic control of renal function.

6. Conclusion

Although numerous studies suggest a connection between renal autonomics and circadian control of solute handling and blood pressure phenotypes, few studies to date have directly focused on these interactions. There is a paucity of specific information available that defines the relationship between autonomic control of kidney function and circadian rhythms as depicted in Fig. 2. In the future, it will be of great value to design animal experiments to specifically probe these questions. Such studies may lead to improved treatment strategies including the effective use of renal denervation and chronotherapy to treat hypertension and kidney disease. Given the ubiquity of telemetry-based measurement of blood pressure in animal studies and ambulatory blood pressure monitoring in clinical trials, reporting of these data as day/night or hourly averages will also greatly increase the clarity of this topic. Attention must also be given to the specific time of day when experimental measurements are conducted in the laboratory. Metabolic and urinary excretion data could be collected every 12 h instead of once per day, although this is problematic in mice that excrete very little urine during their inactive period, which is also the typical time in which acute experiments and tissue collections are made. Further, renal sympathetic nerve experiments may benefit from use of animals entrained on a reverse light schedule so that investigators can measure activity corresponding with rodents' active periods, or telemetry-based renal sympathetic nerve recordings could be utilized. These and other approaches designed with the recognition that circadian factors are likely influencing the outcomes of studies exploring renal function and autonomic control will greatly advance our understanding of these interactions in the years to come.

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