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Circadian Rhythm, Clock Genes and Hypertension: Recent Advances in Hypertension

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Abstract

Accumulating evidence suggests that the molecular circadian clock is crucial in blood pressure (BP) control. Circadian rhythms are controlled by the central clock, which resides in the suprachiasmatic nucleus (SCN) of the hypothalamus, and peripheral clocks throughout the body. Both light and food cues entrain these clocks but whether these cues are important for the circadian rhythm of BP is a growing area of interest. The peripheral clocks in the smooth muscle, perivascular adipose tissue, liver, adrenal gland, and kidney have been recently implicated in the regulation of BP rhythm. Dysregulation of the circadian rhythm of BP is associated with adverse cardiorenal outcomes and increased risk of cardiovascular mortality. In this review, we summarize the most recent advances in peripheral clocks as BP regulators, highlight the adverse outcomes of disrupted circadian BP rhythm in hypertension, and provide insight into potential future work in areas exploring the circadian clock in BP control and chronotherapy. A better understanding of peripheral clock function in regulating the circadian rhythm of BP will help pave the way for targeted therapeutics in the treatment of circadian BP dysregulation and hypertension.

Keywords

Non-dipping; ambulatory blood pressure monitoring; chronic kidney disease; BMAL1; PER1

Introduction

Hypertension is the leading modifiable risk factor for all-cause mortality, with the global burden estimated at 1.4 billion, ~31% of the global adult population[1–3]. Diagnosis mainly relies on in-office or clinic blood pressure (BP) measurements, which do not account for variations in the circadian rhythm of BP[1]. Circadian rhythms are 24-hour oscillations

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that are imperative coordinators to many physiological functions including BP regulation (reviewed in [4]). The daily BP rhythm is characterized by a morning surge on waking with a plateau during the day and a nocturnal decline (a decrease of 10–20% from the average daytime BP). Ambulatory BP monitoring is essential for accounting for this 24-hour BP variation[1,5,6]. Disruption of this 24-hour BP variation is more likely in hypertensive and chronic kidney disease (CKD) patients and is associated with adverse cardiorenal outcomes[7,8]. Abnormal BP rhythms include non-dipping BP (defined as a <10% decrease from daytime to nocturnal BP), reverse dipping (nocturnal risers), and extreme dippers (≥20% between nocturnal and daytime BP). Isolated nocturnal hypertension, defined as nighttime systolic BP ≥120 mmHg and diastolic BP ≥70 mmHg with daytime <135/85 mmHg[9], is usually associated with non-dipping or reverse dipping but can be found in dippers[1]. Nocturnal hypertension and a non-dipping pattern have been shown to increase the risk of hypertension-induced organ damage[10], with the worst outcomes seen in individuals who have both features[11].

Circadian rhythms are controlled by both the central clock, which resides in the suprachiasmatic nucleus (SCN) of the hypothalamus, and peripheral clocks throughout the body. The contribution of peripheral clocks, particularly the kidney clock, to BP rhythm is an active area of research (discussed in detail below). At the molecular level, this is controlled by a cellular clock, which is comprised of four key core clock proteins (CLOCK, BMAL1, PER, and CRY; Figure 1). CLOCK (and its paralogue NPAS2) and BMAL1 (also known as ARNTL) heterodimerize and bind E-box response elements within promoter regions of target genes, including *Period* and *Cryptochrome* (encoding PER1/2/3 and CRY1/2, respectively), and *Ror* and *Nrd1d1/2* (encoding RORα/β/γ and REV-ERBα/β, respectively). In the negative feedback loops, PER and CRY heterodimerize and repress the activity of BMAL1 and CLOCK. ROR and REV-ERB mediate opposing actions on *Bmal1* gene expression[12]. Preclinical research has established that these circadian clock proteins regulate 43% of all expressed genes in mice[13], with >80% of protein-coding genes displaying 24-hour rhythms in expression in non-human primates[14]. Work by various investigators using knockout (KO) rodent models of these core clock genes has brought us closer to understanding how the circadian mechanism contributes to BP regulation. However, the mechanisms underlying non-dipping and abnormally elevated nocturnal BP remain to be fully elucidated.

The purpose of this review is to summarize the most recent advances in both basic and clinical research relating to circadian rhythms, clock genes, and hypertension. Furthermore, we highlight the adverse outcomes of altered circadian rhythm of BP in hypertension and consider future directions from these important findings.

Adverse outcomes of a non-dipping blood pressure profile

High nocturnal BP is often accompanied by a non-dipping profile, but both independently have significance for target organ damage, particularly cardiovascular and renal damage. This has been evident in recent basic and clinical studies published between 2020 and 2021. Wang et al. assessed isolated nocturnal hypertension in CKD patients (n=1484) and found a high proportion of these individuals were non-dippers (individuals with

nocturnal systolic hypertension, 86%; nocturnal diastolic, 71%; nocturnal systolic-diastolic, 86%). Interestingly, there was a higher prevalence of non-dipping with nocturnal systolic and nocturnal systolic-diastolic hypertension. Furthermore, they observed an association between nocturnal systolic hypertension, either alone or in combination with nocturnal diastolic hypertension, and increased risk for cardiovascular events and renal failure in CKD patients[15]. Non-dipping BP has also been associated with proteinuria and progression of renal injury in a rat model of salt-sensitive hypertension[16]. In support of this, Cho et al. reported that patients with controlled hypertension, described in this study as BP managed within a normal range (<140/90 mmHg) by antihypertensive treatment, who were reverse dippers/non-dippers had an increased risk of albuminuria and decreased renal function compared with normal/extreme dippers. Therefore, suggesting monitoring diurnal and nocturnal BP may predict CKD progression, which has been previously reported by Timio et al.[17] and Davidson et al.[7]. However, a limitation of these studies described above was that ambulatory BP was only measured for one 24-hour period. One 24-hour recording with BP measurements at 30 min intervals with ≥70% of expected measurements (20 valid wake (9 AM – 9 PM) and 7 valid asleep (1 AM – 6 AM)) has been reported to validate ambulatory BP data. However, for research purposes, ≥ 2 valid daytime and 1 valid nighttime measurement per hour have been advised[18].

Primary aldosteronism (PA) is reported in 5–10% of hypertensive patients. Patients with PA have been shown to be at high risk of left ventricular hypertrophy due to excessive aldosterone which is at least partly BP independent[19]. Although, BP rhythm in PA has only been recently investigated by Wu et al. who demonstrated that PA patients (n=385) had higher nocturnal systolic BP, along with a non-dipping pattern, compared to patients with essential hypertension (n=385). This non-dipping profile was suggested to be due to excessive aldosterone. There was no difference between age, sex, body mass index, 24-hour BP, daytime BP, or duration of hypertension between these groups. Importantly, the higher nocturnal systolic BP was strongly associated with cardiac damage in PA compared with essential hypertensive patients, emphasizing the importance of measuring ambulatory BP in this case[20].

In contrast, the STANISLAS Cohort study did not find an association between non-dipping BP profile (in normotensive or hypertensive patients) and increased cardiovascular or renal damage[21]. Normotensive and hypertensive individuals who were non-dippers showed no differences between cardiovascular and renal parameters (including carotid intima-media thickness, pulse-wave velocity, left ventricular mass index, left ventricular hypertrophy, eGFR, microalbuminuria, and albuminuria/creatinine ratio) compared with their dipper counterparts[21]. However, the mean 24-hour ambulatory BP in the “hypertensive” participants was <130/90 mmHg. Thus, this group is representative of controlled hypertension by antihypertensive treatment, and the lack of an association between non-dipping BP and detrimental cardiorenal outcomes could be dependent on the level of BP control and whether the individual is truly hypertensive (>130/90 mmHg). It could be hypothesized that good BP control even in non-dipping hypertensive patients could overcome the potential adverse effects of non-dipping BP on target organ damage.

Many studies support this association that nocturnal systolic BP increases the risk of a decline in renal function and increased risk for CV events[22–25], for an extensive review on this association see Hansen et al.[26]. Although differing results have been reported from these studies regarding the link between the non-dipping profile and worsening cardiorenal outcomes. There were no differences in the mean age range (between 50 and 70) in these studies. However, in Redon et al.[22], where non-dipping was not associated with worsening of cardiorenal outcomes, the enrolled participant number was far smaller than other studies and had a shorter follow-up period. The association between non-dipping BP and target organ damage remains controversial due to the populations studied, sample size, and the assessment of specific target organ damage. There is a need for larger analysis addressing the potential association between non-dipping BP and target organ damage, involving ambulatory BP measurements over a longer period of time in a variety of populations spanning various age groups and taking into account whether their hypertension is managed. This is essential to clarify the influence of ethnicity, age, and antihypertensive treatment on the predictive value of non-dipping BP. Overall, these studies highlight the importance of monitoring nocturnal BP and BP rhythm using ambulatory BP measurements and nocturnal BP control for reducing the risk of target organ damage.

A role for peripheral clocks in regulating blood pressure rhythm

Smooth muscle: The mechanisms regulating BP rhythm are not fully understood. Numerous studies have examined the role of circadian clocks using rodent models of null core clock gene mutations, with a particular interest in BMAL1. Male global *Bmal1* KO mice exhibit non-rising BP during the active period, resulting in an overall lower 24-hour BP and loss of diurnal BP rhythm[27]. Efforts have been made to explore the tissue-specific mechanisms underlying the non-rising BP phenotype. Xie et al. demonstrated that smooth muscle BMAL1 was essential for time-of-day variations in phenylephrine- and serotonin-induced vasoconstriction of renal and mesenteric arteries thought to reflect the dampened BP rhythm in smooth muscle-specific *Bmal1* KO male mice[41]. The rhythmicity of the central clock in the SCN remained intact. Although, the extent of the loss of the diurnal BP rhythm was less than the global KO, raising the question - what else is contributing to this non-rising phenotype? It remains unknown what the effect of *Bmal1* deletion in smooth muscle of female mice is.

Perivascular adipose tissue (PVAT): PVAT regulates vascular tone via contractile and anticontractile effects and has been shown to modulate BP *in vivo*, reviewed in [28,29]. Chang et al. investigated the role of the PVAT clock on BP regulation, specifically in brown adipocyte-specific *Bmal1* KO male mice. These mice also had altered expression of other clock genes, including increased *Cry1* and *Npas2*, with decreases in *Per3* and *Rev-erbα*. Brown adipocyte-specific *Bmal1* KO male mice displayed reduced daytime BP, resulting in an extreme-dipper phenotype. The mechanisms behind this are thought to be via BMAL1 regulating transcription of angiotensinogen, leading to increases in angiotensin II levels in PVAT which act on smooth muscle cells within the vasculature to regulate vascular tone and BP rhythm[30]. Again, it is unknown what the role of PVAT BMAL1 in females is, which merits investigation. Obesity is known to cause increased PVAT mass and PVAT dysfunction which correlates with increased BP (reviewed in [31]). Therefore, it would be of interest to

investigate whether the PVAT clock is altered in animal models of obesity and if this impacts BP rhythm.

Liver: Type 2 diabetic patients have increased prevalence of BP rhythm disruption, with up to 70% reported as non-dippers in a cross-sectional study of 20,000 diabetic patients, and a role of the circadian clock has been indicated in the pathogenesis of diabetes[32,33]. Although, little is known about the role of the clock genes in disruption of BP rhythm in diabetes. Hou et al. used the db/db mouse (shown to have a non-dipping phenotype[34]) crossed with PERIOD2::LUCIFERASE knock-in mouse to measure PER2 protein oscillation by bioluminescence in a diabetic mouse model[35]. These diabetic mice were also non-dippers which was suggested to, in part, be due to the advanced phase shift of PER2 in peripheral tissues including the liver, as well as the kidney, and not the central clock in the SCN. Limited studies have explored whether specifically the liver circadian clock plays a role in BP regulation. A recent study has shown altered PVAT-mediated endothelial vascular function in hepatic-specific *Bmal1* KO male mice, with lower systolic BP during the inactive period but no changes in either diastolic BP or heart rate (HR)[36]. This was thought to be due to changes in circulating levels of liver derived mediators, including β-HB and IGF-1.

Adrenal gland: A previous study found an adrenal disorder, characterized by *Hsd3b6*-dependent aldosterone overproduction and differing aldosterone rhythm, in global double *Cry1/2* KO mice compared with controls, which caused these mice to display salt-sensitive hypertension[37]. Whether BP rhythm was affected in these mice and if this is associated with the adrenal clock remains in question. However, it emphasizes the importance of maintenance of daily expression of adrenal *Hsd3b6* by the circadian clock in BP control and its response to a dietary salt challenge. A more recent study by Tanaka et al. investigated the role of the adrenal gland circadian clock in spontaneous hypertensive rats. Several adrenal gland circadian clock genes, such as *Bmal1*, *Per2*, *Per3,* and *Cry1* were phase-advanced compared with control rats. A major role of the adrenal gland is the steroidogenesis of glucocorticoids, mineralocorticoids, and androgens. The circadian expression profile of *StAR*, the rate-limiting enzyme for steroidogenesis, was also found to be phase advanced, as well as serum corticosterone and aldosterone[38]. Both of these steroids have been implicated in BP rhythm[20,39]. This study was observational so further research into the direct effect of the adrenal gland circadian clock on BP rhythmicity would be of interest.

Kidney: Numerous studies have examined the role of the intrinsic renal circadian clock in renal sodium handling to better understand its contributions to BP rhythm. For an excellent and extensive review on the role of the central/renal clock and reactive systems in regulating the rhythm of renal sodium reabsorption to influence BP rhythm, see [40]. As previously mentioned, global *Bmal1* KO mice are non-risers[27], which could be due in part to smooth muscle BMAL1[41]. The global *Bmal1* KO mice also exhibited a loss in diurnal sodium excretion[42]. Efforts have been made to explore the mechanisms behind the lost diurnal sodium excretion in global *Bmal1* KO mice by utilizing mouse models with deletions of *Bmal1* in different regions of the nephron of the kidney. Deleting *Bmal1* in the collecting duct of mice resulted in lowered BP but with no changes in either the diurnal rhythm of BP or sodium excretion. Furthermore, this phenotype was only seen in males, with

females protected[42]. This finding was supported by our own study where we generated a distal nephron-specific *Bmal1* KO mouse model and found lowered BP, with no changes in rhythmicity, in a sex-dependent manner[43]. However, we did find that male mice had reduced renal sodium retention when challenged with a potassium-restricted diet[43]. Overall, suggesting BMAL1 in the distal portions of the kidney of mice contribute to BP regulation independent of changes in BP rhythm in a sex-dependent manner.

Overall, still little is known about the contribution of BMAL1 on diurnal control of renal sodium handling. Using a global *Bmal1* KO rat, Johnston et al. found that male *Bmal1* KO rats had lost the diurnal rhythm of sodium excretion although BP rhythm was intact (unlike the *Bmal1* KO mouse)[54]. Like previous studies, females were protected from this phenotype. This suggests BMAL1 is important for the control of diurnal sodium excretion specifically in male rats, which interestingly appeared dissociated from BP rhythm.

There appears to be species differences with the role of BMAL1, increasing the complexity of understanding its contribution to BP control and rhythm. However, what has been continually reported is that females are protected from BP and/or renal sodium handling changes in *Bmal1* KO rodent models. This has also been demonstrated in female *Per1* KO mice[44]. This leads to questioning whether ovarian sex hormones play a role in the protection of this phenotype. Premenopausal women have a reduced prevalence of hypertension than men and are less likely to present with blunted BP rhythm[45–47]. The prevalence for non-dipping BP was 16 times higher in postmenopausal, compared with premenopausal woman[48]. Therefore, future work to explore the role of ovarian sex hormones in BP rhythm would be of interest.

An alternative approach was conducted by Murata et al. where they suggested the potential contribution of renal clock-regulated proteins, FXR1 and PPAT, in BP rhythm in spontaneous hypertensive rats (SHR)[49]. FXR1 gene and protein levels were reduced in SHR compared with Wistar Kyoto rats (WKY) as controls, which was suggested to impact the proliferation and growth of renal tubular cells. *Ppat* expression was increased in these rats, with no changes in protein levels, and has been linked with vascular toxicity via altering uric acid metabolism. This study was speculative in the role of FXR1 and PPAT in the diurnal variation of electrolyte and water handling, impacting BP rhythm. A caveat of this study was that the SHR model does not have an appropriate genetic control. WKY are often used as controls for this model, as they were derived from the same colony as the SHR. However, it has been reported that WKY may not constitute a single inbred strain[50]. Future studies would be necessary to determine a causal link between altered FXR1 and/or PPAT levels and disruption of BP circadian rhythm and assess strain to strain variability. Furthermore, whether this is sex-dependent would be of interest as the sex of the rats was not provided.

Together, these studies provide evidence for the potential role of the peripheral clock in the regulation of BP rhythm, and for disruption of peripheral clock genes contributing to the non-dipping BP pattern. However, this illustrates the complexity of control of BP rhythm and that, like the pathogenesis of hypertension, this likely involves complex crosstalk between these multiple systems and neurohormonal controllers.

Regulating blood pressure rhythm: the timing of food intake

The central clock receives light input directly from the retina for entrainment of time-of-day and remains resistant to phase perturbations from internal cues, unlike peripheral clocks that are susceptible to adjustments to reflect local metabolic demand (reviewed in [51]). Peripheral clocks have been shown to be entrained by food cues. The question remains, are light and/or food cues important for the circadian rhythm of BP? Zhang et al. addressed this by restricted feeding mice during their inactive phase, causing the BP rhythm to be inverted with no change in average 24-hour BP[52]. Food consumption, over light, entrained BP rhythm in mice as their BP peak was during the feeding period even when fed at various times in constant darkness. Furthermore, the rhythm of PER2 was assessed in tissues following restricted feeding, using the PERIOD2::LUCIFERASE knock-in mouse. PER2 in the SCN (central clock) was not affected, but restricted feeding caused a phase shift in the liver, renal inner medulla, and adrenal gland peripheral clocks. Changes in metabolism via restricted feeding have been previously shown to uncouple peripheral clocks from the central clock in the SCN[53]. Interestingly, the timing of food intake did not entrain renal excretion in mice as urine volume and sodium excretion were unaffected, suggesting a dissociation between BP rhythm and sodium excretion (previously discussed by Johnston et al.[54]). These findings were shown to be independent of BMAL1. However, the role of other clock genes still needs to be explored. This study also observed an inactive phase (day) surge in plasma insulin and an overall increase in inactive phase plasma leptin compared with the active phase in restricted feeding. The contribution of increased nocturnal plasma insulin and leptin levels to the diurnal BP pattern warrants investigation.

What are the implications of this for human health? The benefits of time-restricted feeding (or intermittent fasting) have focussed on weight loss, but recently more benefits have been discovered that are dependent on the time-of-day of the feeding window. As previously mentioned, type 2 diabetic individuals have an increased prevalence of BP rhythm disruption[32,33] along with sleep disturbances[55], possibly in part due to clock gene rhythm disruptions[35]. In db/db mice, restricted feeding to the active phase (between 10 AM and 6 PM) improved their sleep-wake cycle and suggested sleep homeostatic function improvement[56]. Eating during a 6-hour period during the daytime, with a diet provided to ensure maintenance of body weight, in pre-diabetic men with their last meal consumed before 3 PM (to align with circadian rhythms of metabolism) has been shown to improve insulin sensitivity and lower BP, although BP rhythm was not assessed[57]. This lowering of BP was supported by another study following 10-hour restricted feeding in both male and female metabolic syndrome patients[58]. These participants were not restricted to what they could eat during this time and were instructed to continue their regular diet, which had to be recorded during this study. Sex differences were not explored in either of these studies. Interestingly, restricted feeding to the late afternoon/evening, with a diet to ensure maintenance of body weight, increased BP[59]. These studies highlight the potential benefits of time-restricted feeding, specifically during the day, on BP regulation, as well as sleep-wake cycles and insulin sensitivity. However, these studies did not assess the effect of time-restricted feeding on BP rhythm. Therefore, future work in determining the effect of restricted food consumption late at night/during the night compared to during the day on BP

rhythm and nocturnal BP changes in both men and women would be of interest, especially for shift workers.

What can your gut tell you about blood pressure rhythm?

Recent evidence has highlighted a relationship between the circadian clock and the gut microbiota - where the circadian clock can modulate the composition and time-of-day variation of gut microbiota, and microbiota can contribute to the maintenance of clock function (reviewed in [60]). Diurnal changes in the composition and function of the gut microbiota can be modulated by time of feeding and diet[61,62], and diurnal oscillations are abolished in certain gut microbiota in global *Bmal1* KO mice which were sex-dependent[63]. Gut microbiota dysbiosis has been shown to contribute to the development of hypertension[64]. Chakraborty et al. hypothesized that diurnal alterations in gut microbial composition could contribute to a salt-sensitive hypertensive phenotype. This study illustrated that the composition of microbial communities exhibits circadian rhythms that were aligned with BP rhythm in male Dahl salt-sensitive rats. This reshaping of microbiota could be an evolutionary adaptation to ensure the survival of bacterial species, increasing their ability to survive under differing food availability during a 24-hour period. However, it has been suggested that this reshaping alters microbial function, impacting the BP of the host. Furthermore, a high salt diet in these rats elicited a time-of-day variation in specific gut microbes[65]. Future work is needed to test a causal link between gut microbiota rhythm and BP variation. With time of feeding impacting diurnal alterations in the gut microbiota, it would also be of interest to determine if the link between time of restricted feeding and BP rhythm (previously discussed) is associated with diurnal alterations in gut microbiota.

Inflammation

The cellular clock is present in immune cells with many aspects of the immune response exhibiting daily oscillations. These oscillations of immune cell recruitment to tissues are thought to promote tissue recovery[66]. This has been implicated in a rat model of sepsis, where the absence of circadian light cues reduced survival compared with a 12-hour light/dark cycle[67]. This study raises the question of whether there would be a benefit of daily lighting cycles in intensive care units for improving the recovery of patients with sepsis. The circadian rhythm of the immune response can also impact disease development[66]. Clock gene expression has been linked to the expression of pro-inflammatory cytokines and implicated in the development of cancer[68,69]. Over the last decade, there has been increasing evidence for the contribution of the immune system in the pathogenesis of hypertension, recently reviewed by Drummond et al[70]. Although, little is known if there is a role for the clock in different immune cells in the regulation of BP rhythm. A recent study by Yang et al. utilized a mouse model of myeloid cell-specific *Bmal1* deletion showed to have unaltered BP at Zeitgeber times (ZT) 4–5 (~11 am, during the mouse rest phase), using tail-cuff system, and therefore, BP rhythm was not assessed[71]. With previous studies implicating a link between circadian rhythms and the immune response, and the contribution of the immune system in hypertension, improved understanding of rhythms in the immune response and if these rhythms impact BP rhythms would be of great interest.

Autonomic nervous system

Several studies have investigated the role of the autonomic nervous system in non-dipping BP. Studies have suggested a failure to reduce sympathetic and increase parasympathetic activity contributes to a non-dipping BP phenotype[72–74]. However, patients with primary autonomic failure, so very low sympathetic and parasympathetic activities have a high incidence of non-dipping[75]. This suggests that it is the lack of autonomic tone modulation that contributes to non-dipping. The autonomic nervous system also plays a role in renal solute handing[76] and it is postulated that this autonomic control of renal function plays a role in diurnal BP rhythms, although further work is needed to explore these interactions directly. This has been recently reviewed by Becker et al. and highlights future directions in this area including the recognition of time-of-day which can influence renal function and autonomic control outcomes[77].

Recent and ongoing chronotherapy clinical trials

Importantly, the majority (~82%) of U.S. FDA-approved drugs target the products of rhythmic genes found in the mouse[13] and non-human primate[14] and therefore, there may be benefits of timed dosing. Theoretically, chronotherapy has the potential to offer these benefits, although many remain skeptical. The clinical relevance of chronotherapy has been demonstrated in rheumatoid arthritis, as administration of glucocorticoid treatment at night when IL-6 levels peak has been shown to improve the pronounced joint pain seen in the morning in these patients[78], reduce inflammation and improve sleep quality (reviewed in [79]). Furthermore, chronotherapy clinical trials with various cancer treatments, including oxaliplatin, 5-fluorouracil, and folinic acid in metastatic colorectal cancer[80], have shown to be beneficial and less toxic. Over the last decade, Hermida and colleagues have published several articles emphasizing the importance of ambulatory BP monitoring and demonstrating the cardiovascular benefits of nighttime dosing of antihypertensive drugs to patients with non-dipping hypertension[81–83]. A recent report of the Hygia Chronotherapy Trial (ClinicalTrials.gov, NCT00741585) has been published illustrating that routine ingestion of 1 or more antihypertensive drugs (ARB, ACEI, CCB, β-blocker, and/or diuretic) at bedtime in hypertensive patients (n=9552) improved dipper profile and reduced the occurrence of major cardiovascular events, compared with ingestion upon awaking (n=9532)[84]. However, limitations of this study were the use of the PROBE (prospective, randomized, open-label, blinded-end point) design, which can create a source of bias as both the treating physician and participant are aware of their assigned group. Also, participants could be prescribed any and as many medications of the antihypertensive drug classes, potentially for treatment benefit over nighttime dosing benefit. Concerns have been raised over the effect size and conduct of this trial and the *European Heart Journal* has reviewed and published these in the *Discussion Forum* in its 21 April 2020 issue, including responses from the investigators[85–92]. It is also worth noting that the recent HARMONY trial showed no benefits of nighttime dosing with anti-hypersensitive treatment[93], see Table 1. Furthermore, some studies have shown no benefits of nighttime dosing with specific antihypertensive treatment[94] or in specific ethnic groups[95].

Currently, the Treatment in Morning versus Evening (TIME) clinical study (recruitment details published in [96,97]) based in the United Kingdom is in progress, involving the

PROBE based design. Recruitment includes more than 20000 participants already on antihypertensive treatment instructed to take their medication either in the morning or at night over a 4-year period, with cardiovascular outcomes assessed. Although, ambulatory BP monitoring will not be reported in this trial, and therefore unlikely to provide further evidence for a benefit for chronotherapy for hypertension. In the Effect of Antihypertensive Medication Timing on Morbidity and Mortality (BedMed) trial (ClinicalTrials.gov, NCT02990663), based in Alberta Canada, hypertensive patients (estimated n=3400) are again instructed to take their antihypertensive medication either in the morning or at night over an average of a 4-year period. Interestingly, the same group of investigators are completing a similar clinical trial as above, however specifically in an elderly population of 1200 participants (BedMed-Frail, NCT04054648). The completion of both BedMed trials is due by the end of 2022. Recent and ongoing clinical trials for chronotherapy in hypertension have been summarized in Table 1.

There are studies, although with small sample sizes, that have explored morning versus evening dosing of specific antihypertensive drugs or combination antihypertensive therapy, reviewed in [98]. The bulk of these studies suggested benefits of evening dosing over morning, but some highlighted benefits of morning administration or no differences with timing of dosage. These differences could relate to the specific pharmacokinetic profile of antihypertensive drugs. Therefore, the pharmacokinetics of drugs for chronotherapy need to be considered[99]. Previous studies have investigated the pharmacokinetic profile of antihypertensive drugs after morning or evening administration, reviewed in[100]. The calcium channel blocker, amlodipine, has been shown to have a shorter time to reach maximum plasma concentration (T_{max}), greater mean peak plasma concentration (C_{max}), and longer half-life after evening oral dosing compared with morning dosing in both normotensive and hypertensive subjects, indicating enhanced absorption of amlodipine when administered at night. This pharmacokinetic profile correlated with significant reductions in BP and HR in hypertensive patients following evening dosing[101]. There have also been reports highlighting sex-specific differences in pharmacokinetics of antihypertensive drugs[102–104]. For example, women have been shown to exhibit higher C_{max} to β-blockers metoprolol and propranolol due to increased absorption and slower clearance via CYP2D6[105,106].

Although these trials provide promise, uncertainty remains over the benefit of chronotherapy for hypertension, and larger trials across multiple ethnic groups with specific antihypertensive drug classes and gender differences investigated are needed to determine who will benefit from chronotherapy. If chronotherapy is not deemed to be superior to the current standard of care for hypertension, it may be beneficial in correcting loss of BP rhythm, which alone is a risk factor for cardiovascular mortality[107]. Overall, the optimal method to test chronotherapy in hypertension is using ambulatory BP monitoring and using drugs with half-lives that are appropriate for nighttime use.

Shift working

Shift work, defined by working hours out with the typical working time of 7 AM – 6 PM, has been associated with increased risk of hypertension, as well as cardiovascular disease and type 2 diabetes[108]. A meta-analysis of 27 observational studies found a significant

association between shift work and hypertension, especially in male shift workers. There was no association between specifically shift work at night, i.e., the Graveyard shift, and a higher risk of hypertension however, data for this was limited[109]. Although, this was not the case when assessing the risk of hypertension in a cohort of 2151 workers from US shift/night workers in manufacturing facilities. Workers with mostly night work with frequent rotations had a 4-fold high risk for hypertension, with the highest rates of hypertension in individuals who worked 95–100% night work[110]. Regarding the risk of CKD in shift workers, the KNHANES study explored the association between shift work and CKD in both male and female manual labor daytime and shift workers (n=3504). This study illustrated female shift workers had an increased risk of CKD, with no association in male workers[111]. BP was measured in these individuals with no significant difference between daytime and shift workers. The BP rhythm was not assessed in these individuals. Hill et al. used a pre-clinical model to investigate how circadian disruption affects kidney function and found that shifting the light cycle to mimic shift work in male hypertensive rats disrupted rhythms in renal excretion and caused an acceleration of renal injury marker excretion[112]. Whether this could influence the pathogenesis of hypertension and CKD remains to be explored.

There have been limited studies on the impact of acute or long-term shift work on BP rhythm. A recent meta-analysis of 50 publications between 1980 and 2018 revealed BP dipped during the sleep period in shift workers but these studies varied widely of shift work type, shift schedules, and regularity of BP monitoring[113]. Further research is needed to investigate the impact of acute and long-term shift work on ambulatory BP in shift workers with and without hypertension.

Conclusion and future perspectives

Together these findings prompt many ongoing questions. Whether non-dipping BP worsens cardiorenal outcomes remains in debate, but the recent studies illustrated in this review have provided evidence for adverse outcomes in patients that have non-dipping nocturnal hypertension. This was particularly evident in CKD patients, suggesting the circadian BP profile could predict the progression of CKD. Therefore, highlighting the importance of monitoring 24-hour BP rhythm using ambulatory BP monitoring and that restoring a BP dip should be recognized as an important aspect of BP control. Although, the mechanisms behind the circadian rhythm of BP are not fully understood, what is clear is that it involves multiple organ systems, illustrated in Figure 2. A better understanding of clock function in various peripheral clocks will help pave the way for targeted therapeutics in the treatment of hypertension. Time of feeding and what we are eating, which can affect our gut microbiota composition, could have long-term impacts on our BP rhythm. A consideration for future research would be whether the timing of the consumption of specific foods would have differing effects on BP. Does a higher salt load at night have implications on non-dipping BP? Considering the findings regarding time-restricted feeding, it would be of interest to investigate whether the timing of the consumption of high salt meals at lunchtime rather than dinnertime had influences on BP. This would also be particularly relevant for shift workers where late-night eating is more common.

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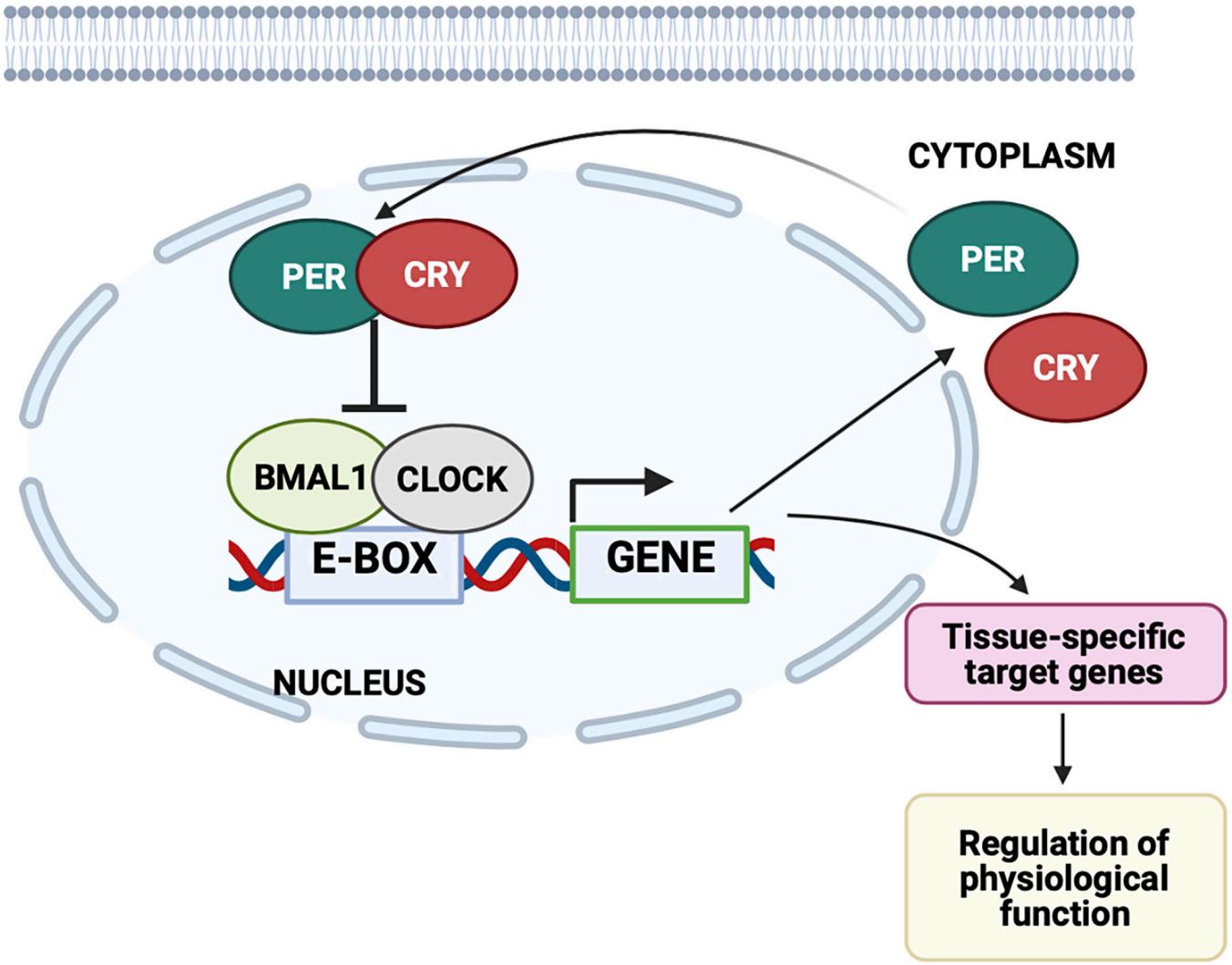

Figure 1. Core components of the circadian clock.

CLOCK and BMAL1 heterodimerize and bind E-box response elements within promoter regions of target genes, including *Period* and *Cryptochrome* (encoding PER1/2/3 and CRY1/2, respectively). In the negative feedback loops, PER and CRY heterodimerize and repress the activity of BMAL1 and CLOCK. This clock mechanism regulates tissue-specific target genes to regulate many physiological processes. Diagram created with Biorender.com.

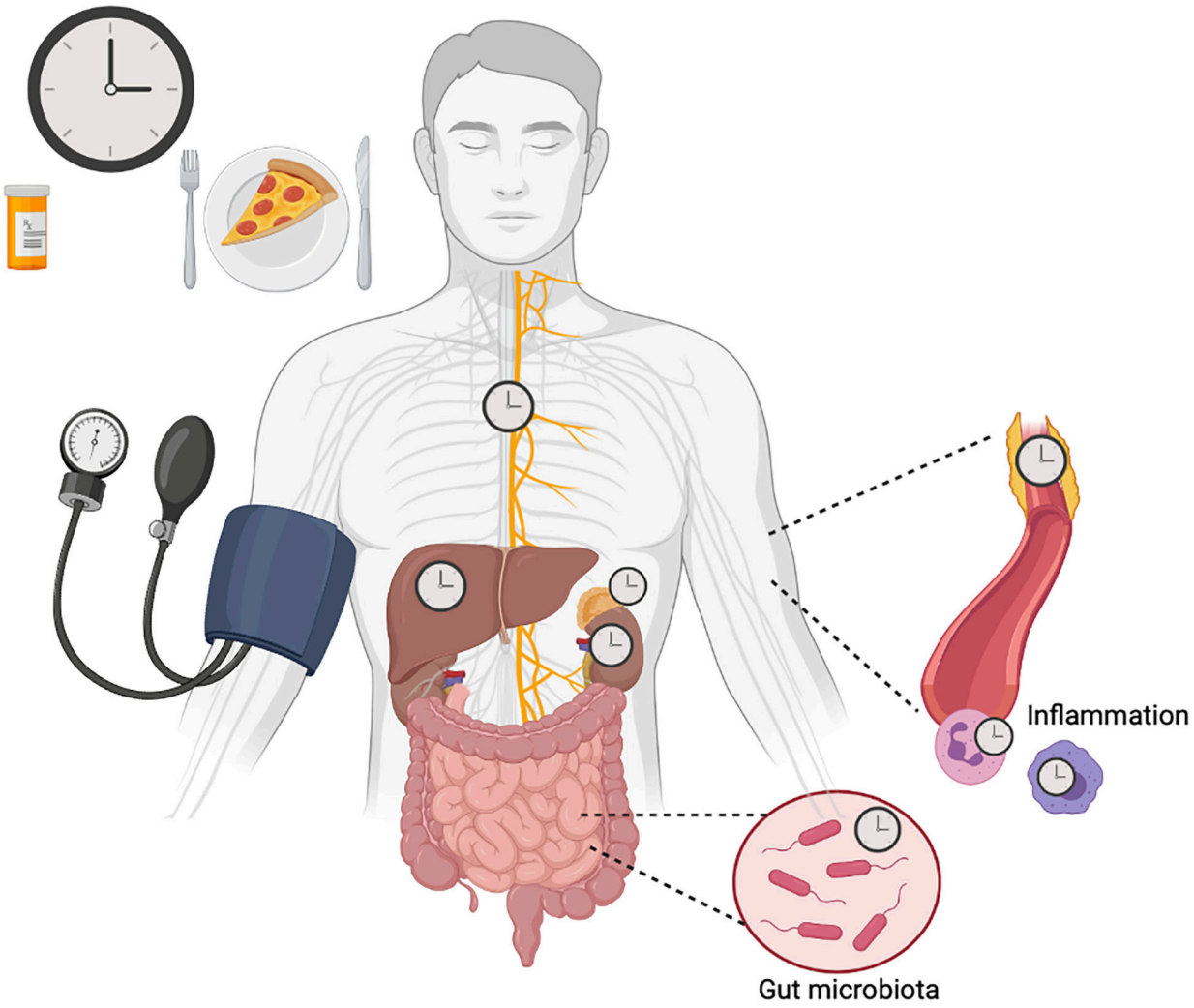

Figure 2. Cellular circadian clocks throughout the body, entrained by food cues, contributing to the circadian rhythm of blood pressure.

Blood pressure has a 24-hour cycle, peaking during the day and dipping by 10–20% during the night. Studies in rodents and humans suggest peripheral clocks within the vasculature, liver, adrenal glands, kidneys, microbiota in the gut, immune system, and autonomic nervous system contribute to regulation of the circadian rhythm of blood pressure (BP). These peripheral clocks can be entrained by food cues therefore, time-of-day feeding could be important for BP rhythm. Dysregulation of the circadian rhythm of BP is associated with adverse cardiorenal outcomes and increased risk of cardiovascular mortality. There are ongoing clinical trials to determine if chronotherapy will be beneficial for hypertension management and this should be expanded to whether it can correct any losses of BP rhythm. Diagram created with Biorender.com.

Table 1.

Recent and in progress clinical trials for chronotherapy in hypertension.

Clinical trial	Participants details	Duration	Study design	In progress?	Results	Reference
Hellenic-Anglo Research into Morning or Night Antihypertensive Drug Delivery (HARMONY; NCT01669928)	103 hypertensive patients (59 men/44 women, 61.8 ± 10.3 years of age)	24 weeks	Patients assigned to ingest ≥ 1 hypertension medication in the morning (6AM-11AM; *n*=51) or in the evening (6 PM-11 PM; *n*=52) for 12 weeks then crossed over for remaining 12 weeks. 24 h ambulatory BP monitoring.	No	No significant differences in 24 h, daytime, or nighttime SBP between morning and evening administration of antihypertensive medication.	93
Hygia Chronotherapy (NCT00741585)	19084 hypertensive patients (10614 men/8470 women, 60.5 ± 13.7 years of age)	6.3 years median patient follow-up	Patients assigned to ingest ≥ 1 hypertension medication at bedtime (*n*=9552) or upon awakening (*n*=9532). 48 h ambulatory BP monitoring.	No	Reduced nighttime SBP, lower prevalence of non-dipping BP and 45% reduction in primary cardiovascular disease outcome in bedtime ingestion patients, compared with morning dosing.	84
Treatment in Morning versus Evening (TIME; UKCRN1707)	21116 hypertensive patients	4 years	Patients assigned to ingest ≥ 1 hypertension medication in the morning or evening. No ambulatory BP monitoring. Primary end point is hospitalization for the composite end point of non-fatal MI/stroke or vascular death.	Yes		96
Effect of Antihypertensive Medication Timing on Morbidity and Mortality (BedMed; NCT02990663)	3440 hypertensive patients (estimated enrollment)	4 years	Patients assigned to ingest ≥ 1 hypertension medication in the morning or evening.	Yes		
BedMed Frail (NCT02990663)	1200 hypertensive patients who are residents in a participating long term care facility (estimated enrollment)	2 years (estimate)	Patients assigned to ingest ≥ 1 hypertension medication in the morning or evening.	Yes		