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Review

Circadian Clock: A Non-Negligible Role in Hypertension-Associated Ischemic Stroke

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Abstract

Hypertension and ischemic stroke (IS) are prevalent circulatory system disorders. Notably, hypertension is a major risk factor for IS, with approximately 70% of IS patients having a documented history of hypertension. Meanwhile, studies have demonstrated that antihypertensive therapy reduces IS recurrence risk by 19–22%; however, nearly half of patients still exhibit inadequate blood pressure (BP) control. The circadian clock, an endogenous timing system synchronized to the 24-hour light–dark cycle, exerts multiple protective effects on the cardiovascular and cerebrovascular systems through spatiotemporal regulatory mechanisms, including the regulation of diurnal BP rhythms, suppression of neuroinflammation, maintenance of blood–brain barrier (BBB) integrity, modulation of coagulation functions, and attenuation of vascular endothelial cell (EC) senescence. These insights provide novel perspectives for the prevention and treatment of hypertension-associated IS. This review elaborates on the composition and functional mechanisms of the circadian clock and discusses the role of circadian rhythm in hypertension and IS comorbidity, particularly how circadian dysregulation contributes to the elevated incidence and severity of IS in hypertensive individuals. Furthermore, this review critically evaluates circadian-based therapeutic strategies, including chronopharmacological approaches and lifestyle interventions, while acknowledging that most of these strategies remain in preclinical or early clinical investigation. These insights may provide novel perspectives for future research into the prevention and management of hypertension-associated IS.

Keywords: circadian clock; hypertension; ischemic stroke; circadian clock genes; immunomodulation; chronotherapy

1. Introduction

Systemic arterial hypertension, commonly referred to as hypertension, is characterized by persistently elevated blood pressure (BP) within the circulatory system [1]. Clinically defined as sustained systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg, hypertension is among the leading causes of cardiovascular disease (CVD) and premature mortality worldwide [2]. Ischemic stroke (IS) arises from focal cerebral hypoperfusion due to etiological factors such as hypertension, atherosclerosis, or embolism, leading to a temporary interruption of arterial blood flow and subsequent focal neurological deficits, such as hemiparesis [3]. Clinically, IS diagnosis is based on acute neurological deficits consistent with brain infarction confirmed through imaging, making it a primary cause of long-term disability and mortality globally. Hypertension significantly contributes to both initial and recurrent IS, with approximately 70% of IS patients reporting a documented history of elevated BP [4]. Nearly half of these patients continue to demonstrate suboptimal BP control, and evidence indicates a dose-dependent relationship between IS and BP levels [5]. Two systematic reviews involving 10 and 8 randomized controlled trials, respectively, demonstrated that antihypertensive pharmacotherapy substantially reduces the relative risk of stroke recurrence by 22% and 19% [6,7]. Therefore, effective BP control remains the cornerstone strategy for primary IS prevention in hypertensive patients [8]. Emerging evidence reveals that hypertension and IS share common pathophysiological mechanisms, including inflammation-driven vascular remodeling, endothelial dysfunction, and blood-brain barrier (BBB) disruption [9,10]. Notably, these processes are subject to circadian clock regulation.

The circadian clock, also referred to as circadian rhythms, is an endogenous, self-sustained timing system synchronized to the 24-hour light–dark cycle and functions as a molecular timekeeping hub. It drives adaptive temporal regulation of physiological and behavioral processes, enabling organisms to align internal biological states with environmental demands by performing appropriate functions at optimal times [11]. The circadian clock regulates

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rhythmic fluctuations in numerous physiological processes over a 24-hour period, including nutrient levels (e.g., glucose, fatty acids, and triglycerides) and hormone concentrations (e.g., insulin and glucocorticoids) across cells, tissues, and organs, while also modulating cardiovascular function and immune system dynamics [12]. Research syntheses have confirmed that the circadian clock contributes to BP regulation and ameliorates hypertension, whereas circadian disruption exacerbates cardiorenal complications and increases CVD-related mortality risk [13]. In parallel, accumulating evidence indicates that the circadian clock influences IS prognosis; stable circadian rhythms promote neurorehabilitation, whereas circadian disruption aggravates stroke severity and increases the risk of long-term neurological sequelae [14]. This review summarizes the molecular architecture of the circadian clock and critically examines its pathophysiological association with hypertension-associated IS. We focus on the following aspects: (i) circadian regulation of BP homeostasis through peripheral clocks in the vasculature, kidneys, perivascular adipose tissue, and adrenal glands; (ii) circadian influences on IS pathogenesis, including coagulation function, neuroinflammation, and neurovascular unit integrity; (iii) circadian-based therapeutic strategies, with explicit differentiation between established clinical practices, promising translational approaches, and experimental interventions. By integrating these perspectives, we aim to clarify how circadian dysregulation may contribute to the elevated incidence and severity of IS in hypertensive individuals and to identify potential targets for future chronotherapeutic development.

2. Circadian Clock

2.1 Composition and Structure

Circadian clocks are evolutionarily conserved molecular oscillators present across diverse life forms, including bacteria, fungi, algae, plants, and mammals, including humans. These endogenous timekeeping systems synchronize physiological and behavioral activities with the Earth's 24-hour rotational cycle [15]. Although no single definitive experiment marks the origin of circadian rhythm research, pioneering studies conducted by Colin Pittendrigh in Drosophila and by Jürgen Aschoff in humans during the 1950s are widely regarded as foundational to the field of chronobiology [11]. The circadian clock is an endogenous oscillatory system that exerts rhythmic regulatory effects on organisms [16,17,18]. Although circadian rhythms are generated independently of light, they can be entrained by light signals to maintain temporal synchronization. In addition, the circadian clock exhibits temperature compensation, thereby preserving rhythmic stability across a range of environmental temperatures [18]. The circadian clock coordinates numerous physiological processes throughout the daily cycle, including sleep-wake patterns, body temperature rhythms, and hormonal oscillations [19,20]. The circadian timing system consists of a central pacemaker and multiple peripheral oscillators [21]. The central circadian clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus and functions as the master pacemaker. Specialized retinal ganglion cells detect environmental light signals and transmit this information to the SCN, which subsequently synchronizes peripheral oscillators through neural and humoral pathways [22]. Peripheral oscillators are distributed across organs such as the heart, liver, spleen, lungs, and kidneys. These oscillators receive regulatory signals from the SCN through circulating hormones, metabolic signals, and systemic cues, including fluctuations in body temperature, collectively forming an integrated circadian oscillator network [23]. Moreover, peripheral oscillators can autonomously reset their phase in response to external zeitgebers (time cues), such as feeding cycles and metabolic stimuli, thereby maintaining tissue-specific circadian rhythms independently of direct SCN regulation [24].

2.2 Molecular Mechanism

The molecular mechanism underlying the circadian clock centers on a transcriptional-translational feedback loop operating over approximately 24 hours, characterized by an inherent time-delay effect (Fig. 1). This mechanism continuously cycles away from and back toward equilibrium, generating rhythmic oscillations through intrinsic feedback within the transcriptional-translational circuitry. Critically, this feedback exclusively modulates circadian clock proteins via cell-autonomous mechanisms, independent of intercellular interactions [25]. The core molecular components of the mammalian circadian clock consist primarily of transcription factors that regulate gene expression [26]. These transcription factors form an asymmetric heterodimer composed of circadian locomotor output cycles kaput (*CLOCK*) and brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein 1 (*BMAL1*) in the cytoplasm. This *CLOCK*:*BMAL1* heterodimer acts as the activating arm of the circadian clock and constitutes the molecular basis of the mammalian circadian oscillator [27]. *CLOCK* proteins function within pacemaker neurons of the SCN and represent essential elements driving intracellular circadian rhythms [28]. *BMAL1* is similarly a crucial component of the central circadian clock, exhibiting high-level expression in specific brain regions and driving synchronized peripheral oscillations in tissues such as muscle and visceral organs [29]. During the daytime, the *CLOCK*:*BMAL1* heterodimer binds to E-box enhancers in the promoters of target genes, activating transcription of Period1 (*Per1*) and Cryptochrome1 (*Cry1*) and initiating a positive feedback loop (the *Per1* and *Cry1* promoters themselves contain E-box elements) [30]. The PER and CRY proteins gradually accumulate until reaching a critical threshold, after which they dimerize (PER:CRY complex) and translocate into the nucleus at night. Once in the nucleus, PER:CRY directly in-

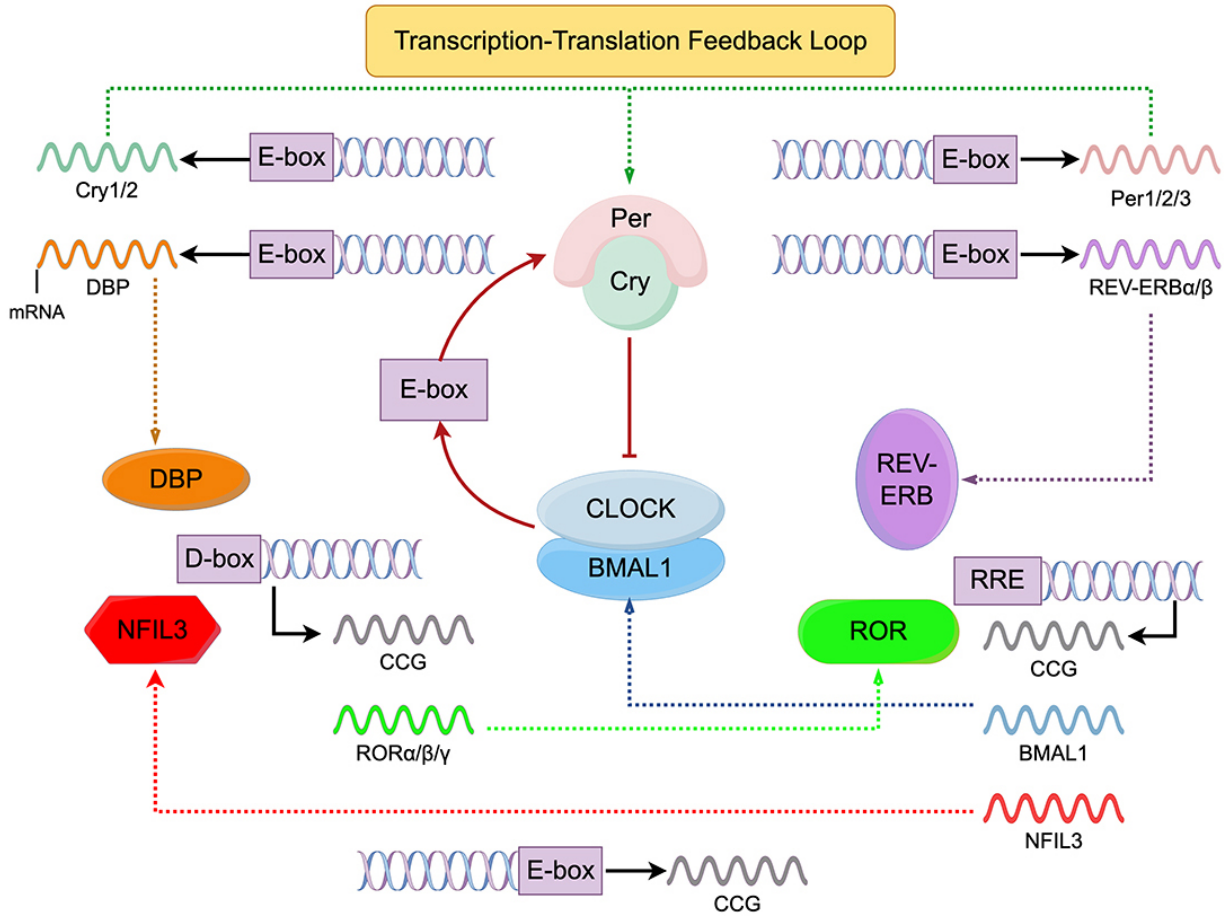


Fig. 1. Transcription-translation feedback loop. In the core feedback loop, *CLOCK–BMAL1* transcription factors drive the expression of their negative regulators, PER and CRY proteins. PER and *CRY* subsequently inhibit *CLOCK–BMAL1* activity, thereby repressing their own transcription. Upon sufficient degradation of PER/CRY, *CLOCK–BMAL1* initiates a new transcriptional cycle. Concurrently, *CLOCK–BMAL1* induces expression of REV-ERBα/β, which antagonizes ROR*α*/*β*/*γ*-mediated transcription of *BMAL1*, and DBP, which activates D-box-containing genes, including ROR*α*/*β*/*γ*. NFIL3, targeted by both REV-ERB and ROR, suppresses D-box-dependent transcription. All loops collectively regulate clock-controlled genes (CCGs) that mediate circadian outputs. *CLOCK*, circadian locomotor output cycles kaput; *BMAL1*, brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein 1; PER, Period; CRY, Cryptochrome1; REV-ERBα/β, nuclear receptor subfamily 1 group D member 1/2; ROR, retinoic acid receptor-related orphan receptor; DBP, D-box-binding protein; NFIL3, nuclear factor, interleukin 3 regulated. Created in Figdraw.

hibits *CLOCK*:*BMAL1*-mediated transcription, completing the negative feedback loop and suppressing transcription [31]. Following ubiquitin-dependent degradation of the PER:CRY repressor complex by specific E3 ubiquitin ligases (SCF*β*-TrCP and SCFFBXL3), transcriptional repression is lifted, allowing the *CLOCK*:*BMAL1* heterodimer to initiate new rounds of transcriptional activation and restart the circadian cycle [32]. This rhythmic transcriptional cycling exemplifies the gating property of the circadian clock [33]. *CLOCK*, *BMAL1*, *Per1*, and *Cry1* constitute the core positive-negative feedback loop of the circadian clock. Concurrently, nuclear receptors REV-ERB*α* and REV-ERB*β*, encoded by NR1D1 and NR1D2, respectively, form an auxiliary regulatory loop that interacts with the core circadian clock. Retinoic acid receptor-related orphan receptors (RORs), comprising RORα, RORβ, and RORγ, regulate BMAL1 transcription through competitive binding to ROR response elements in the BMAL1 promoter. Genes within cis-regulatory regions co-targeted by *BMAL1*, REV-ERB*α*, and REV-ERB*β* are significantly enriched for circadian and metabolic functions [34]. Additional transcription factors, such as RAR-related orphan receptors (RORs), maintain circadian rhythm through competitive binding with REV-ERBs at ROR response elements within the *BMAL1* promoter region. *BMAL1* transcription is enhanced by ROR binding and suppressed when REV-ERBs bind to these sites [35,36].

During cardiac differentiation, detectable oscillations emerge as the human circadian clock develops in embryonic stem cells [37]. Numerous cardiovascular and cerebrovascular functions, including endothelial function, thrombosis formation, and heart rate, are regulated by the circa-

dian clock [37,38,39]. Studies have shown that deletion of *BMAL1* disrupts circadian rhythms, induces premature aging and cardiomyocyte enlargement, and shortens lifespan in mice [40]. Disruption of circadian rhythms also causes BP dysregulation, and evidence supports a causal link between *BMAL1* polymorphisms and hypertension in humans [29]. Moreover, a high-salt diet suppresses *BMAL1* expression, resulting in disrupted circadian rhythms, elevated BP, increased susceptibility to atrial fibrillation, and myocardial fibrosis in Dahl salt-sensitive hypertensive rats [41]. Whether similar *BMAL1* suppression occurs in human salt-sensitive hypertensive patients is unknown. Furthermore, the circadian clock regulates thrombogenic factors (vWF, plasminogen activator inhibitor-1 (PAI-1)) and fibrinogen levels; circadian disruption elevates these factors, accelerating thrombosis in the context of circadian dysfunction caused by *BMAL1* deficiency [42]. Vascular smooth muscle cell relaxation involves endothelium-derived relaxing and hyperpolarizing factors, derived primarily from endothelial nitric oxide synthase (eNOS) and reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. These enzymes are directly regulated by endothelial circadian mechanisms. Consequently, disruption of circadian rhythms induces vascular endothelial dysfunction [43]. Circadian clock genes modulate endothelial cell (EC) functions, including cell cycle progression, proliferation, migration, and angiogenesis [44]. Dysregulation of these genes accelerates EC senescence, impairs BBB integrity, and ultimately contributes to cerebrovascular pathology, as demonstrated experimentally [45]. Additionally, the circadian clock gene REV-ERBα functions as a key regulator of immunity, mitochondrial biogenesis, metabolism, inflammatory responses, and fibrosis [46]. Its cardioprotective roles and underlying mechanisms have been mechanistically validated in CVD contexts [47]. Collectively, these experimental studies in cellular and animal models support an association between circadian disruption and cardiovascular risk factors, although a definitive causal relationship in humans remains to be established through prospective clinical investigations. These molecular insights form the basis for understanding how circadian dysregulation contributes to cardiovascular and cerebrovascular disorders, as discussed in subsequent sections.

3. The Correlation Between the Circadian Clock and Hypertension-Associated Ischemic Stroke

3.1 The Connection Between the Circadian Clock and Hypertension

The primary goal of hypertension treatment is to maintain BP within an optimal range; it is now widely acknowledged that BP exhibits circadian rhythmicity [48]. BP increases upon waking (morning surge), peaks in the afternoon, and declines during nighttime rest, a phenomenon termed “dipping BP” that follows a 24-hour circadian pattern [49]. This circadian rhythm arises from environmental influences and behavioral factors affecting the circadian clock. The circadian regulation of BP involves several key physiological sites (Fig. 2). Peripheral circadian clocks in the vasculature, kidneys, and endocrine tissues significantly regulate BP homeostasis, and their dysregulation profoundly impacts cerebrovascular integrity and IS pathogenesis, as detailed below.

3.1.1 Vascular Endothelial and Smooth Muscle Cells

Traditionally, the SCN has been considered the central regulator of circadian BP rhythms. However, Xie et al. [50] demonstrated through *in vivo* experiments that smooth muscle cell-specific knockout (KO) of *BMAL1* (but not in cardiomyocytes) disrupts BP circadian rhythms and reduces overall BP. Crucially, this effect occurs independently of SCN-regulated locomotor activity, indicating that BP rhythmicity is influenced by both central and peripheral clocks. In the context of hypertension, where vascular smooth muscle cell hypercontractility and endothelial dysfunction are prevalent, circadian disruption may exacerbate these pathological changes, thereby increasing IS susceptibility. Experimental studies have shown that disruption of core circadian clock genes, including Bmal1 and Clock, impairs vascular endothelial function in mice [51]. Separately, smooth-muscle-specific deletion of Bmal1 disrupts blood pressure circadian rhythms and reduces blood pressure in mice [50]. In addition, circadian clock gene disruption can alter thrombogenesis, as demonstrated in experimental models [52]. These findings suggest that circadian clock dysregulation may contribute to vascular dysfunction and thrombosis, potentially linking chronic hypertension to IS, although direct clinical evidence in hypertensive IS patients remains to be established. Restoring *BMAL1* expression specifically in vascular smooth muscle cells may therefore represent a promising therapeutic approach for normalizing BP rhythms in hypertensive patients.

3.1.2 Kidney

Numerous studies have demonstrated that intrinsic renal circadian clocks regulate sodium handling, balancing excretion and reabsorption [53]. Research reviews on circadian renal sodium regulation suggest that circadian clocks coordinate excretion and reabsorption through predictive adaptations (maximizing daytime sodium reabsorption), reactive responses (adjusting excretion based on real-time sodium concentrations and blood volume changes), and endocrine signaling. Non-dipper blood pressure patterns likely represent circadian dysregulation in renal sodium handling [54]. Substantial evidence shows that KO or knockdown of kidney-specific *BMAL1* genes abolishes circadian rhythms in sodium excretion. Notably, these effects appear sex-specific, manifesting exclusively in males [55,56,57]. Consequently, investigating the role of ovarian function and estrogen signaling in circadian BP regula-

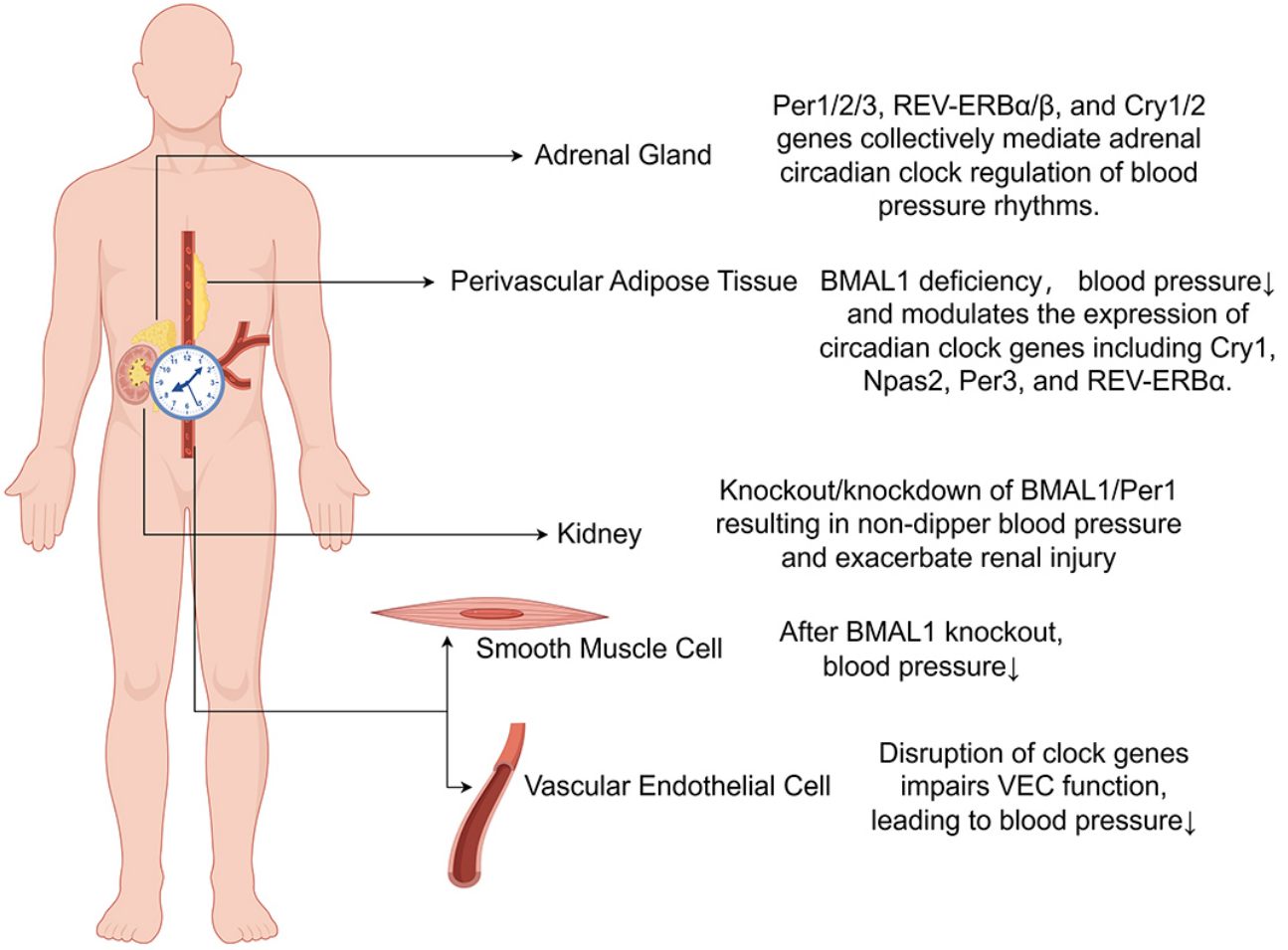


Fig. 2. Circadian clock regulation of BP. Downward arrows indicate reductions in corresponding indicators. BP, blood pressure. VEC, vascular endothelial cell. Created in Figdraw.

tion is a significant area for future research. Renal-specific deletion of *Per1* via cadherin-Cre similarly enhances renal sodium reabsorption, elevates aldosterone levels, and alters gene expression in kidneys and adrenal glands [58]. Additional research has demonstrated that *Per1* KO in Dahl salt-sensitive rats exacerbates salt-sensitive hypertension and related renal injury [59]. These effects are mediated by the renin–angiotensin–aldosterone system (RAAS) and potentially involve interactions with catecholaminergic pathways. These experimental findings indicate that renal circadian clocks contribute to sodium homeostasis and BP regulation. In hypertensive patients, particularly those with salt-sensitive hypertension or chronic kidney disease, circadian dysregulation of renal sodium handling may promote nocturnal BP elevation and increase IS susceptibility. However, whether targeted restoration of renal circadian rhythms can reduce IS risk in hypertensive patients remains to be determined through clinical trials. The observed sex-specific effects also highlight the need for gender-stratified analyses in future studies.

3.1.3 Perivascular Adipose Tissue

Conventionally, adipose tissue was viewed primarily as protective for adjacent organs; however, accumulating evidence now recognizes it as an endocrine organ [60,61]. Obesity closely associates with vascular disease, suggesting adipose tissue involvement in the pathogenesis of these conditions [62,63]. Among adipose tissues, perivascular adipose tissue (PVAT), which directly surrounds blood vessels, is particularly relevant to vascular pathology. PVAT is heterogeneous and metabolically active, extending beyond simple structural support. In addition to adipocytes, PVAT contains ECs, fibroblasts, immune cells, and other cell types [63]. PVAT interacts with the vasculature through paracrine signaling, contributing to both physiological homeostasis and pathological alterations in the cardiovascular system [64,65]. PVAT influences BP regulation through the secretion of soluble factors (e.g., anti-contractile and anti-inflammatory mediators), mechanical vascular support, buffering of vascular stress, and adipocyte-specific metabolic activities [66]. Chang et al. [67] demonstrated that PVAT-specific *BMAL1* expression prevents excessive declines in resting-phase BP in mice.

Brown adipose tissue-specific *BMAL1* KO mice exhibit significantly reduced resting-phase BP, displaying a "super-dipper" hypertension phenotype. This phenomenon is mediated by the *BMAL1*–angiotensinogen (*Agt*)-angiotensin II (Ang II) signaling axis, which targets vascular smooth muscle cells. Specifically, *BMAL1* regulates angiotensinogen transcription, elevating Ang II levels within PVAT. Increased Ang II acts directly on vascular smooth muscle cells, dynamically modulating vascular tone and circadian BP rhythms. Additionally, these mice exhibit altered expression of other circadian genes, including *Cry1*, *Npas2*, *Per3*, and REV-ERBα [68]. It suggests that PVAT represents a potential target for circadian-based interventions. The circadian clock within PVAT may represent a previously unrecognized mechanism linking metabolic dysfunction, hypertension, and cerebrovascular vulnerability. In hypertensive patients with metabolic dysfunction, PVAT circadian dysregulation may promote abnormal vascular tone and exacerbate BP variability, thereby increasing IS risk. However, whether modulation of PVAT circadian rhythms can normalize BP patterns or reduce IS incidence in hypertensive patients remains speculative and requires translational investigation.

3.1.4 Adrenal Gland

The adrenal gland, an essential component of the endocrine system, plays a critical role in regulating various physiological processes, including metabolism, electrolyte balance, and particularly BP control [69]. In 1898, Tigerstedt and Bergman discovered a renal pressor substance now recognized as renin [70]. Renin release triggers a cascade resulting in the generation of angiotensin II (Ang II) and aldosterone through the well-characterized renin-angiotensin-aldosterone system (RAAS). The RAAS represents the primary mechanism by which the adrenal gland influences BP, primarily promoting its elevation [71]. Consequently, the RAAS remains extensively investigated for the development of comprehensive and effective antihypertensive treatments. A study conducted in spontaneously hypertensive rats (SHR) revealed generally reduced expression of *Per1*, *Per2*, *Per3*, and REV-ERBα/β genes in adrenal glands compared to controls. These animals exhibited a phase advancement in core clock and clock-controlled gene expression and overexpression of the *E4bp4* gene independent of the RORA signaling pathway [72]. Earlier investigations by Ota et al. [73] into adrenal clock functions demonstrated that arrhythmic mice lacking the clock genes *Cry1* and *Cry2* (Cry-null mice) exhibited disrupted circadian BP rhythms yet maintained BP within normal physiological limits. When exposed to a high-salt diet, these Cry-null mice developed elevated plasma aldosterone concentrations, decreased renin activity, and suppressed RAAS expression, thereby triggering salt-sensitive hypertension [74]. Subsequently, the authors proposed that salt-sensitive hypertension in these animals could be attributed to excessive aldosterone production mediated by *Hsd3b6* and altered circadian patterns of aldosterone secretion [75]. Circadian regulation of adrenal steroidogenesis may influence the hypertensive patient's vulnerability to cerebrovascular events through temporal modulation of RAAS activity.

In summary, these findings illustrate that peripheral circadian clocks are indispensable regulators of BP rhythms. Furthermore, the inherent complexity of circadian BP regulation suggests intricate connections between circadian mechanisms and hypertension pathogenesis. Despite the documented influence of circadian clocks in various tissues and organs on BP control, the precise mechanisms and direct causal pathways remain incompletely understood, largely due to complex interactions among circadian components. Whether chronotherapeutic targeting of adrenal circadian rhythms can improve BP control in hypertensive patients remains an open question requiring clinical investigation. Since most evidence comes from experimental models, further studies, including translational studies in hypertensive cohorts with circadian phenotypes, will be critical to elucidate these pathways and identify tissue-specific therapeutic targets.

3.2 Circadian Clock Influences on Ischemic Stroke Pathogenesis in Hypertension

Circadian clocks are distributed throughout the body and regulate numerous physiological and pathological processes, including known cardiovascular risk factors. Cerebrovascular diseases such as IS, which are closely associated with these cardiovascular risk factors, also exhibit prominent circadian rhythms [76]. Research indicates that among patients with ischemic stroke (IS), symptom onset occurred during the morning in 19.2%, during the day in 32.6%, during the evening in 27.3%, and at night in 20.9% of cases [77]. Patients with nocturnal symptom onset had larger ischemic core volumes at hospital admission than those with daytime onset (median, 40.2 mL vs. 33.8 mL). Furthermore, ischemic core growth was significantly faster at night than during the day (adjusted $p = 0.01$) [77]. Circadian disruption can lead to extreme dipping of BP [48], disrupted cortisol secretion [78], elevated triglycerides [79], glucose intolerance, and insulin resistance [80], all of which potentially contribute to IS development. Curtis et al. [81] demonstrated that knockout of core circadian genes, such as *BMAL1* or *CLOCK*, reduces mean arterial pressure and disrupts sympathetic–adrenal axis stress responses, thereby increasing IS incidence. Physiological factors significantly influencing IS include arterial BP, coagulation function, and neuroinflammatory responses [82]. Disruption of the neurovascular unit (NVU) integrity is central to IS pathophysiology, causing BBB leakage, glial activation, neuronal injury, and chronic inflammation, thus creating a microenvironment that impairs recovery. Consequently, circadian regulation of the NVU also significantly influences IS progression. Furthermore, abnormalities in BP rhyth-

Table 1. Summary of mechanisms by which circadian clocks regulate neuroinflammatory responses through various cell types.

Immune cell type	Related clock genes	Mechanism
Brain ECs	*BMAL1*	The circadian oscillations expressed by neuronal activity can regulate gene expression in ECs, thereby mediating ion transport across the BBB, thus influencing BBB permeability [97].
Astrocytes	*BMAL1*, REV-ERBα/β, *Npas2*/*CLOCK*	Loss of clock genes can affect astrocyte morphology, including but not limited to cell proliferation and process dysfunction [98,99,100].
Microglia	REV-ERBα, *Per2*, *BMAL1*, *CLOCK*, *Cry1*	*BMAL1* promotes LPS-induced IL-6 expression in microglia by regulating the IL-6 gene promoter [104]. REV-ERBα is negatively correlated with IL-6 levels [101], and its receptor agonist disrupts the microglial circadian clock, reducing phagocytic and pro-inflammatory functions [105]. Loss of *BMAL1* leads to decreased transcriptional levels of pro-inflammatory cytokines produced by microglia and upregulates the expression of antioxidant and anti-inflammatory factor genes [103]. Normally, *Per2* is negatively correlated with IL-1β and TNF-α levels [102].
Pericytes	*BMAL1*	Pericytes play a key role in regulating neuroinflammation. Disrupting the endogenous circadian clock in pericytes using *BMAL1*-targeting shRNA reduces their viability and increases apoptosis [106].

micity induced by circadian disruption have been established as both a pathogenic factor for IS onset and a contributor to adverse post-stroke outcomes [68]. The following sections examine these factors sequentially, with explicit attention to the hypertensive context.

3.2.1 Coagulation Function

The predominant etiological factor underlying IS is thrombus formation mediated by atherosclerosis-associated coagulation dysfunction [83]. The fibrinolytic system serves as a critical endogenous defense mechanism against pathological thrombosis [84]. Evidence indicates that this system is also regulated by circadian rhythms. In patients with CVD and circadian disruption, impaired fibrinolytic activity, altered platelet function, and abnormal coagulation parameters have been observed. This phenomenon is likely attributable to increased plasminogen activator inhibitor-1 (PAI-1) levels induced by circadian dysregulation, thereby increasing susceptibility to thrombotic events [85,86]. However, whether direct modulation of circadian coagulation rhythms can reduce IS incidence in hypertensive patients is currently unknown. Ohkura et al. [87] demonstrated through *in vivo* murine experiments that euglobulin clot lysis time (ECLT), a measure of fibrinolytic potential, exhibits circadian rhythmicity. *CLOCK* and CRY proteins participate in fibrinolytic regulation through modulation of PAI-1 transcription. Furthermore, mice harboring mutations in core circadian clock genes exhibit prolonged ECLT and loss of its rhythmic oscillation.

3.2.2 Neuroinflammation

Among the physiological factors implicated in IS, neuroinflammation exerts a profound influence on disease onset, recurrence, and prognosis [88]. Following IS onset, hemolytic products within the subarachnoid space and/or brain parenchyma trigger neuroinflammatory responses, initiating immune cell activation and infiltration and promoting the release of pro-inflammatory cytokines, chemokines, and reactive oxygen species, ultimately leading to neuronal injury and neurological dysfunction [89]. Persistent neural injury disrupts the BBB and increases its permeability, representing a central pathological feature of IS [90,91]. Moreover, in hypertensive patients, chronic neuroinflammation and pre-existing BBB disruption due to endothelial senescence and vascular remodeling may exacerbate post-stroke inflammatory injury and impair recovery. Consequently, preservation of BBB integrity and prevention of EC activation are critical therapeutic objectives in IS management [92]. The presence of a circadian clock within the BBB was first demonstrated in Drosophila melanogaster by Long and Giebultowicz [93]. In addition, the brain contains a complex and dynamic network integrated with the BBB that protects the central nervous system, termed the NVU [94]. The NVU primarily consists of brain ECs, astrocytes, microglia, neurons, and pericytes, all of which are regulated by circadian rhythms [95]. Furthermore, cell-specific circadian dysregulation in immune cells can trigger inflammatory responses [96]. The following sections summarize the mechanisms through which these cell types influence IS and the roles of the circadian clock in these processes (Table 1, Ref. [97,98,99,100,101,102,103,104,105,106]).

3.2.2.1 Brain ECs. The circadian clock in brain ECs within the BBB maintains BBB stability and integrity by regulating specific ions and molecules, including Mg^{2+} and ATP. Zhang et al. [107] demonstrated through *in vivo* and *in vitro* experiments that the BBB circadian clock gene *BMAL1* regulates intracellular magnesium cycling through transcriptional control of *TRPM7*, enhances BBB xenobiotic efflux efficiency, and modulates transporter protein activity. Notably, xenobiotic accumulation in the brain exhibits an opposite pattern in mice and Drosophila melanogaster, consistent with their opposing activity rhythms. Neuronal activ-

ity can also regulate BBB permeability, thereby influencing BBB transport function [108]. Womac et al. [109] demonstrated experimentally that ATP levels exhibit circadian-like oscillations with an average period of approximately 23.7 hours. More recently, studies have confirmed that neuronal activity displays circadian oscillations and regulates clock gene expression in brain ECs, thereby mediating neuronal activity-dependent regulation of BBB efflux transport [97]. In hypertensive patients, circadian disruption of brain EC function may compound pre-existing BBB dysfunction, potentially increasing IS severity and impairing recovery.

3.2.2.2 Astrocytes. Glial cells, including astrocytes, microglia, and oligodendrocytes, are the most abundant cell types in the central nervous system [110]. Astrocytes are widely distributed throughout the cerebral cortex and regulate neurotransmitter uptake, immune responses, and BBB integrity through changes in their morphology, thereby promoting neuronal survival. These morphological changes are commonly associated with glial fibrillary acidic protein (GFAP) expression levels [111,112]. In hypertensive patients, astrocyte activation and glial scar formation following IS are more pronounced, potentially due to pre-existing endothelial dysfunction. Circadian regulation of astrocyte morphology and function may therefore influence the extent of post-stroke injury and the efficiency of tissue repair in this population. Recent studies have demonstrated that astrocytes in the cerebral cortex, spinal cord, and SCN exhibit circadian oscillations [113,114,115]. Studies on the relationship between astrocyte morphology and circadian regulation have shown that disruption of astrocytic circadian clocks in *BMAL1* knockout (KO) mice alters cellular morphology. Specifically, *BMAL1* regulates astrocyte hypertrophy through coordinated cell-autonomous mechanisms and minor non-cell-autonomous signaling from neurons [98]. Ali et al. [111] demonstrated that astrocyte-specific deletion of *BMAL1* suppresses *Cttn* expression and reduces Rho-GTP activation, thereby affecting the morphology of fine cellular protrusions and leading to functional abnormalities in these structures. Compared with control mice, *BMAL1* KO mice generally require more than 10 weeks to exhibit significant GFAP upregulation across multiple brain and spinal cord regions, suggesting that increased GFAP expression is mediated primarily through *BMAL1*-dependent cell-autonomous regulation [116]. In addition to *BMAL1*, other circadian clock components, including REV-ERBα/β and NPAS2/CLOCK, also regulate astrocyte function through distinct mechanisms. REV-ERBα/β signaling can modulate the expression of pronociceptive molecules in astrocytes [99], while disruption of CLOCK/NPAS2-related circadian regulation is associated with increased GFAP immunoreactivity and astrocyte activation [100], also regulate GFAP expression and astrocyte proliferation through distinct mechanisms. Furthermore, brain-derived neurotrophic factor (BDNF) has been shown to play an important role in coordinating astrocyte–neuron interactions and mediating circadian regulation of iron metabolism [117]. In patients with hypertension-associated IS, disruption of the circadian regulation of astrocyte function may impair BBB restoration and exacerbate neuroinflammation during the subacute phase.

3.2.2.3 Microglia. Microglia are innate immune cells comprising approximately 5–12% of the total cell population in the brain, representing a critical component of the brain's immune system [118]. Characterized by significant plasticity, microglial phenotypes primarily include resting, activated, and proliferative states [119]. In their resting state, microglia predominantly regulate synaptic connectivity and maintain homeostasis within the central nervous system. However, upon inflammatory stimulation, microglia become activated and undergo phenotypic shifts to facilitate immune responses. Activated microglia produce pro-inflammatory cytokines, recruiting additional immune cells, and subsequently transition to a proliferative phenotype after inflammation resolution [120]. Pro-inflammatory cytokines secreted by activated microglia include tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) [121]. Numerous recent studies have demonstrated circadian rhythmicity in the expression of these cytokines. Under physiological conditions, microglial processes exhibit increased numbers and length during the dark phase [122]. Yi et al. [123] reported that microglial numbers and process complexity in the mediobasal hypothalamus (MBH) increased during the dark phase in lean mice. This rhythmic pattern was accompanied by increased TNF-α gene expression, whereas IL-1β and IL-6 expression did not show the same daily rhythmicity. REV-ERBα negatively regulates IL-6 expression, and its expression levels inversely correlate with IL-6 in intact spinal cord tissue [101,102]. Additionally, circadian oscillations of TNF-α and IL-1β in the intrathecal space of the intact spinal cord negatively correlate with *Per2* expression [102]. Microglia in the cortical region exhibit intrinsic circadian clock regulation and substantial circadian oscillations in cathepsin S transcription. Deficiency of cathepsin S abolishes circadian variations in synaptic activity and dendritic spine density in cortical neurons [124]. *BMAL1* deficiency in mice reduces microglial transcription of pro-inflammatory cytokines while concurrently upregulating antioxidant and anti-inflammatory gene expression [103]. *BMAL1* in microglia binds to the IL-6 gene promoter and is required for lipopolysaccharide (LPS)-induced IL-6 expression [104]. The REV-ERBα receptor agonist SR9011 disrupts intrinsic microglial circadian rhythms by modulating signaling pathways (reducing expression of *BMAL1*, *CLOCK*, *Per2*, and *Cry1*), thereby attenuating microglial phagocytosis and pro-inflammatory responses [105].

3.2.2.4 Pericytes. Pericytes, located along cerebral capillaries, contribute to the regulation of cerebral blood flow by relaxing in response to neuronal activity and constricting capillaries under ischemic conditions [125]. They also play an essential role in maintaining EC homeostasis and modulating neuroinflammatory responses [125,126]. Thus, pericytes significantly influence IS prognosis [127]. Extensive astrocyte activation induces pericyte dysfunction, thereby increasing BBB permeability and causing leakage [116]. Mastrullo et al. [106] demonstrated that pericytes possess intrinsic circadian clocks, and the disruption of the pericyte clock via *BMAL1*-targeted shRNA reduces pericyte viability and enhances apoptosis. In hypertensive patients with pre-existing BBB disruption, dysregulation of the circadian clock in pericytes may further compromise cerebrovascular integrity and increase the risk of hemorrhagic transformation following thrombolytic therapy. However, research on the interactions between pericytes and circadian rhythms remains limited, and the underlying mechanisms require further elucidation. Investigating these interactions represents a promising direction for future studies examining circadian influences on the cerebrovascular endothelium.

Nevertheless, it remains unclear whether interventions targeting the circadian clock in pericytes can improve functional outcomes in this population, as all evidence is derives from experimental models. Understanding post-stroke pathophysiological progression is critical to IS management, and the role of circadian rhythms in modulating this progression warrants considerable attention. Clinical research assessing biomarkers and sleep architecture in patients demonstrated that circadian disruption contributes to sleep-wake cycle disturbances. These sleep-wake cycle disturbances may represent modifiable risk factors for IS incidence, recurrence, and poor post-stroke outcomes [128], suggesting that circadian restoration may have particular therapeutic value in hypertension-associated IS survivors.

4. Circadian Clock-Based Prophylaxis and Treatment of Hypertension-Associated Ischemic Stroke

Despite decades of advancements in public education and therapeutic approaches to hypertension, epidemiological studies indicate that approximately 23.2% of Chinese adults (≥18 years) have hypertension. Alarmingly, only 46.9% of hypertensive individuals are aware of their condition, and merely 15.3% achieve effective BP control [129]. Poorly controlled hypertension promotes IS incidence and recurrence through three interconnected mechanisms: increased vascular shear stress, induction of endothelial dysfunction, and disruption of the BBB [130]. Thus, hypertension and IS remain major global health burdens. As discussed previously, circadian rhythms influence both conditions. Furthermore, hypertension and IS share common pathological mechanisms, including BBB disruption driven by neuroinflammation and endothelial aging [10,131]. Consequently, circadian clock modulation represents a promising therapeutic target for managing hypertension-associated IS. Circadian clock-targeted interventions for hypertension and IS primarily function via the following mechanisms:

4.1 Immune Response Modulation

Excessive accumulation of immune cells within blood vessels (particularly in perivascular adipose tissue [PVAT]), the heart, kidneys, or brain can induce inflammatory responses, leading to organ damage and contributing to hypertension or IS [132]. Recent studies have demonstrated that immune cells from both the innate and adaptive immune systems contribute to hypertension, and that modulation of specific immune cell populations can influence blood pressure and hypertension-associated inflammation and target-organ injury [133,134,135,136]. Although the pathophysiological relationship between inflammation and hypertension is increasingly understood, the molecular mechanisms underlying immunomodulation-driven hypertension control remain relatively unexplored. Similarly, immunomodulation is critically important for IS, where targeted immunomodulatory therapies aim to reduce neuroinflammation-induced brain injury and improve neurological outcomes [137]. Beyond their roles in stroke-related inflammation, immune cells also contribute to brain development and the maintenance of normal brain function and homeostasis [138]. Both innate and adaptive immune responses display circadian oscillations, which underlie their temporal regulation [139]. Advancements in circadian clock research reveal that the circadian clock acts as an immune regulator, enhancing organismal fitness by reducing immunological costs and improving immune efficiency [140]. Most circadian immune regulatory mechanisms involve clock genes at the molecular level. The core circadian gene *BMAL1* functions as a central mediator connecting circadian rhythms and immunity, primarily by suppressing inflammatory responses [139]. The following mechanisms have been identified primarily in experimental models and may inform future therapeutic development: Kitchen et al. [141] demonstrated that *BMAL1* depletion in macrophages induces actin cytoskeletal remodeling, activating RhoA signaling and altering actin dynamics, thus enhancing antibacterial responses. Additionally, *BMAL1* regulates macrophage oxidative stress pathways by modulating *Nrf2* (an antioxidant regulator) mRNA expression and suppressing IL-1β production; *BMAL1* deficiency decreases *Nrf2* activity, resulting in pathological IL-1β overproduction [142]. Ly6C^{hi} inflammatory monocytes exhibit circadian rhythmicity, and myeloid-specific *BMAL1* deletion elevates inflammatory chemokine expression and disrupts Ly6C^{hi} monocyte rhythms, thereby increasing susceptibility to acute and chronic inflammatory conditions in mice [143]. Mouse studies have also identified a dual regulatory mechanism in neutrophils, in which *BMAL1*-mediated

chemokine induction promotes neutrophil aging; paradoxically, this aging state antagonizes another chemokine pathway, facilitating neutrophil extravasation and enhancing antibacterial defense [144]. The clock gene REV-ERBα is recognized as a crucial regulator of microglial activation and neuroinflammation in mice. Microglial immune responses in the mouse hippocampus exhibit circadian characteristics, and loss of REV-ERBα disrupts these rhythms, leading to dysregulated NF-κB signaling and spontaneous microglial activation. Consequently, this elevates proinflammatory factor transcription and promotes astrocyte proliferation [145]. Sugimoto et al. [146] demonstrated that astrocyte-specific deletion of *Per1* increases secretion of IL-6 and CCL2, exacerbating neuroinflammatory responses. Although no clinically approved immunomodulatory drugs specifically targeting hypertension-associated ischemic stroke (IS) are currently available, a phase II clinical trial in patients with acute stroke showed that treatment with an IL-1 receptor antagonist was well tolerated and reduced circulating inflammatory markers, including C-reactive protein and interleukin-6 [147]. However, the trial was not designed to assess stroke incidence, and this intervention does not specifically target circadian mechanisms. Existing evidence supports the role of circadian rhythms in immune modulation via clock genes, suggesting therapeutic benefits for hypertension and IS. Nevertheless, the precise mechanisms through which circadian-regulated immune responses alleviate hypertension-associated IS remain unclear, and translational studies are required to validate these experimental observations in human populations.

4.2 Chronotherapy

Chronotherapy is a therapeutic strategy based on the circadian regulation of physiological and pathological processes and can be classified into pharmacological and non-pharmacological interventions [148]. It modulates circadian rhythms through these interventions and strategically times drug administration to maximize efficacy and minimize adverse effects [149]. These approaches are complementary rather than mutually exclusive. Chronotherapy has demonstrated beneficial or protective effects in CVD, including hypertension and IS [150]. However, current research into chronotherapy remains limited, and standardized chronotherapeutic protocols specifically for hypertension-associated IS are yet to be established, highlighting the need for further investigation and clinical validation.

4.2.1 Drugs-Circadian Clock

Accumulating evidence shows that pharmacological responses are governed by circadian rhythms, a phenomenon known as chronopharmacology, which comprises chronopharmacodynamics and chronopharmacokinetics [151,152,153]. Circadian variations in membrane microviscosity and permeability significantly influence molecular and cellular responses by modulating interactions between pharmacologically active compounds and their molecular targets [154]. Consequently, the pharmacodynamic effects of certain drugs, such as heparin [155] and famotidine or ranitidine [156], vary substantially depending on administration timing. Research indicates that the absorption, distribution, metabolism, and elimination of numerous drugs also follow circadian patterns [157]. Regardless of drug class, administration route, or dosage regimen, chronopharmacokinetics governs active drug concentrations in target tissues [158]. Studies have identified agonists of the clock gene REV-ERB as effective modulators of mitochondrial biogenesis [159], sleep disturbances [160], and metabolic disorders [161]. Although direct mechanisms linking these agonists to hypertension or IS treatment remain unconfirmed, documented benefits for muscle and sleep regulation suggest potential cardiovascular advantages. Furthermore, the circadian clock in PVAT regulates local angiotensinogen transcription via the *BMAL1–Agt* axis, indicating that chronotherapy could indirectly regulate peripheral clocks to normalize BP and reduce vascular stress [68]. Thus, pharmacological modulation of circadian clock genes represents a promising therapeutic direction. However, relevant studies remain scarce, necessitating comprehensive basic, translational, and clinical investigations to validate efficacy. Various antihypertensive medications, including β-adrenergic receptor antagonists, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and diuretics, demonstrate chronobiological characteristics. Chronotherapeutic combinations with these agents effectively regulate 24-hour BP profiles in hypertensive patients [162]. A prospective clinical study demonstrated that each 5-mmHg reduction in mean asleep systolic blood pressure was associated with a 17% reduction in cardiovascular risk, highlighting the potential importance of nocturnal blood pressure control in cardiovascular prevention [163]. Hermida et al. [164] showed that bedtime administration of ACEIs/ARBs optimized nocturnal BP rhythms, significantly enhancing cardiovascular protection and demonstrating the greater effectiveness of chronotherapy in hypertension management. Similarly, Zeng et al. [165] demonstrated that bedtime administration of a fixed-dose combination of amlodipine (5 mg) and hydrochlorothiazide (25 mg) resulted in lower nocturnal and 24-hour mean blood pressure and a greater reduction in the morning blood pressure surge than morning administration. Bedtime dosing also increased the proportion of patients who converted from a non-dipper to a dipper blood pressure pattern. The role of antiplatelet therapy in preventing acute IS recurrence is also significant. Studies have demonstrated that bedtime administration of aspirin, the most common antiplatelet agent, provides superior platelet inhibition compared to morning dosing, potentially reducing the incidence of early morning cardiovascular events

Table 2. Circadian-based therapeutic strategies for hypertension-associated IS: evidence classification.

Category	Intervention	References
Established clinical relevance	Bedtime administration of antihypertensive agents (ACEIs/ARBs, CCBs)	[164,165,188]
	Bedtime aspirin administration	[166,167]
Promising but not yet validated	Melatonin supplementation	[174,175,176,177]
	Light therapy for circadian entrainment	[179,180]
	Structured exercise programs	[182,183,184]
Experimental/preclinical	REV-ERBα agonists	[105,159,160,161]
	BMAL1-targeted vascular gene therapy	[50]
	Pharmacological modulation of microglial circadian clocks	[145]

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers.

[166,167]. Emerging evidence implicates glucocorticoids in sleep disturbances not only through elevated BP but also through circadian clock disruption in the SCN. This disruption occurs via serotonin depletion or reduced neurotransmitter activity within the SCN. In peripheral clocks, glucocorticoids modulate circadian rhythms through *Per1*/*Per2* signaling pathways. Such circadian disruption-induced sleep disorders subsequently elevate BP and cardiovascular risk, creating a vicious cycle that exacerbates hypertension-associated IS and other CVDs [168]. Although statins are first-line therapeutics for CVD, the mechanistic basis for statin-induced sleep disturbances remains unclear. Although BMAL1 is essential for transcriptional adaptation of skeletal muscle and peripheral tissues to endurance exercise training [169], its role in statin responses, particularly statin-associated sleep disturbances, remains unclear. Melatonin, widely recognized for regulating mammalian responses to changes in ambient light, has gained considerable attention for its potential role in managing circadian rhythm-related sleep disorders. Nevertheless, current evidence does not conclusively classify melatonin as a definitive "sleep hormone" [170]. Sleep disorders, however, constitute significant risk factors for hypertension and IS [171]. Although melatonin is not essential for maintaining circadian clock homeostasis, it influences clock synchronization [172,173]. Since 2000, melatonin has been known to confer neuroprotective effects against cerebral ischemia in rat glial cells [174]. Melatonin protects primary cultures of rat cortical neurons against NMDA-induced excitotoxicity and hypoxia/reoxygenation injury, in part by limiting free-radical-mediated cellular damage [175]. Additionally, melatonin promotes astrocyte-mediated protection of brain ECs in IS [176]. When combined with other stroke therapies, melatonin effectively mitigates IS-related brain injury and behavioral impairments [177]. Current melatonin research remains primarily at the preclinical stage, focusing on underlying mechanisms, while translational and clinical evidence is limited. Nonetheless, these findings indicate promising therapeutic targets for future circadian rhythm-related research.

4.2.2 Non-Pharmaceutical Circadian Clock Interventions

Chronotherapy encompasses not only pharmacological interventions but also circadian rhythm regulation through lifestyle modifications and environmental adjustments in disease management. As the central circadian pacemaker, the SCN mediates photic signal transmission to regulate sleep–wake cycles and other physiological systems [178]. Accordingly, light therapy can therapeutically modulate circadian rhythms, and studies have demonstrated its efficacy in affective disorders and sleep–wake disturbances, with potential benefits for improving outcomes in hypertension-associated IS [179,180]. Lifestyle factors, particularly dietary habits and sleep patterns, are also critically important because of their close association with circadian rhythms. Alterations in these factors can rapidly disrupt circadian clock homeostasis [181]. Research has shown that appropriately timed exercise can shift circadian phase, as reflected by changes in dim-light melatonin onset (DLMO) in humans [182]. Similarly, afternoon exercise improves sleep quality in older adults and thereby facilitates maintenance of circadian homeostasis [183,184]. Time-aligned feeding patterns reinforce metabolic regulation and prevent dysregulated metabolic responses induced by irregular eating behaviors. Consequently, circadian disruption increases susceptibility to metabolic disorders, such as obesity, while simultaneously elevating the risk of hypertension-associated IS [185,186]. Circadian rhythms and sleep are bidirectionally regulated, such that disruption of one system inevitably affects the other. Studies have demonstrated that shift workers frequently experience circadian misalignment and sleep disturbances, both of which are independently associated with adverse metabolic and cardiovascular outcomes [187]. Consequently, maintaining healthy sleep hygiene and dietary patterns may stabilize circadian homeostasis and reduce the incidence of hypertension, IS, and their comorbidity.

Collectively, these findings indicate that circadian-based interventions for hypertension-associated IS span a broad spectrum of evidence maturity. To clarify this heterogeneity for clinical and research audiences, Table 2 (Ref.

[50,105,145,159,160,161,164,165,166,167,174,175,176,177,179,180,182,183,184,188]) summarizes these strategies according to their current evidence classification.

5. Summary and Future Perspectives

As a master regulator of behavioral and physiological rhythms, maintenance of circadian clock homeostasis is essential for normal physiological function. Disruption of circadian rhythmicity induces systemic maladaptation and increases susceptibility to disorders, including hypertension and IS, through multiorgan dysregulation. This review summarizes the current understanding of the molecular architecture of the circadian clock and its pathophysiological association with hypertension-associated IS. Accumulating evidence supports circadian-based interventions as promising therapeutic strategies, thereby providing new perspectives for targeted chronotherapy. Accordingly, circadian clock regulation emerges as an important modulator in the management of hypertension-associated IS.

Although evidence indicates that circadian-timed administration can optimize the pharmacodynamics and pharmacokinetics of existing therapies for hypertension and IS, clinical translation remains limited. Furthermore, robust clinical trials are required to translate findings from both mechanistic studies and preliminary clinical investigations into validated therapeutic approaches for patients with hypertension-associated IS. To date, no chronotherapeutic agents targeting core circadian clock components have progressed beyond the preclinical stage. Current clinical management primarily relies on non-pharmacological entrainment strategies, including regulated meal timing, optimized sleep hygiene, and structured exercise programs, to restore circadian alignment. Nevertheless, chronotherapy retains considerable translational potential in both behavioral and pharmacological domains. Therefore, chronotherapeutic strategies targeting core clock genes and proteins represent an important research frontier and may provide promising molecular targets for the management of hypertension-associated IS.

In summary, circadian clock regulation constitutes a critical axis in cardiovascular and cerebrovascular pathophysiology and provides a novel conceptual framework for managing hypertension-associated IS through chronotherapeutic approaches. Future studies aimed at elucidating circadian mechanisms underlying hypertension-associated IS, together with the development of precision chronotherapies, may substantially improve patient management and therapeutic outcomes.

Abbreviations

Ang II, Angiotensin II; BBB, Blood-brain barrier; *BMAL1*, Brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein-1; BP, Blood pressure; *CLOCK*, Circadian locomotor output cycles kaput; *Cry1*, Cryptochrome1; DBP, D-box-binding protein; NFIL3, nuclear factor, interleukin 3 regulated; ROR, retinoic acid receptor-related orphan receptor; ECLT, Euglobulin clot lysis time; ECs, Endothelial cells; eNOS, Endothelial nitric oxide synthase; GFAP, Glial fibrillary acidic protein; IS, Ischemic stroke; NVU, Neurovascular unit; PAI-1, Plasminogen activator inhibitor-1; *Per1*, Period1; PVAT, Perivascular adipose tissue; RAAS, Renin-angiotensin-aldosterone system; SCN, Suprachiasmatic nucleus.

Author Contributions

M-HS and YY are co-first authors and contributed equally to this work. M-HS: Conceptualization, writing—original draft, investigation (literature screening and data extraction). YY: Conceptualization, writing—original draft, investigation (literature search and data extraction). H-BY: Investigation (literature screening and data extraction), visualization, writing—review & editing. X-PL: Investigation (literature search and data extraction), formal analysis, data curation, writing—review & editing. Y-HW: Investigation (literature screening and data extraction), visualization, writing—original draft, writing—review & editing. Y-YT: Conceptualization, methodology, supervision, funding acquisition, writing—review & editing. QZ: Conceptualization, methodology, project administration, supervision, funding acquisition, writing—review & editing. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The authors declare no conflicts of interest.

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