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CLINICAL REVIEW

Circadian mechanisms of 24-hour blood pressure regulation and patterning

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SUMMARY

In most persons, blood pressure (BP) rises slowly during late sleep, increases rapidly upon morning awakening and commencement of diurnal activity, exhibits two – morning and afternoon/early evening – daytime peaks, shows a minor midday nadir, and undergoes a decline during nighttime sleep by 10–20% in systolic BP and somewhat lesser amount in diastolic BP relative to wake-time means. Nyctohemeral cycles of ambient temperature, light, noise and behaviorally driven temporal patterns in food, liquid, salt, and stimulant consumption, mental/emotional stress, posture, and physical activity intensity plus circadian rhythms of wake/sleep, pineal gland melatonin synthesis, autonomic and central nervous, hypothalamic-pituitary-adrenal, hypothalamic-pituitary-thyroid, renin-angiotensin-aldosterone, renal hemodynamic, endothelial, vasoactive peptide, and opioid systems constitute the key regulators and determinants of the BP 24 h profile. Environmental and behavioral cycles are believed to be far more influential than circadian ones. However, the facts that the: i) BP 24 h pattern of secondary hypertension, e.g., diabetes and renal disease, is characterized by absence of BP fall during sleep, and ii) scheduling of conventional long-acting medications at bedtime, rather than morning, results in much better hypertension control and vascular risk reduction, presumably because highest drug concentration coincides closely with the peak of most key circadian determinants of the BP 24 h profile, indicate endogenous rhythmic influences are of greater importance than previously appreciated.

Introduction

Around-the-clock blood pressure (BP) monitoring, recently recommended by the U.S. Preventive Services Task Force as the reference standard to substantiate diagnosis of hypertension when suggested by daytime clinic cuff measurement [1], reveals the mostly predictable and appreciable day/night variation of both systolic and diastolic BP (SBP/DBP). The 24 h pattern typical of diurnally active normotensive and uncomplicated hypertensive persons displays: small BP increase before the termination of nighttime sleep, striking rise upon morning awakening, two daytime peaks – the first 2–3 h after awakening and the second, usually prominent one, in the middle or late activity span, small mid-afternoon nadir, and decline by 10–20% in SBP, and of lesser amount in DBP, during sleep relative to wake-time means [2]. Such nyctohemeral variation is substantiated, although often of diminished amplitude, in recumbent normotensive and hypertensive individuals [3,4], with quantitative differences between elderly men and women [5] and those with fixed heart rate [6]. The contribution of cyclic changes in the environment – temperature, humidity, noise, and light – and behavior – food, liquid, salt, and stimulant consumption, emotional/mental stress, posture, and physical activity intensity – to the 24 h BP pattern is well established [7–12]. However, there is less awareness of the many endogenous circadian rhythms that play an important role (Table 1) and that ought to be taken into consideration when prescribing hypertension therapy and its optimal timing [13–18]. Thus, the subject of this comprehensive review is the contribution of innate

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Abbreviations

ABPM	ambulatory blood pressure monitoring
ACE	angiotensin converting enzyme
ACEIs	angiotensin converting enzyme inhibitors
ACTH	adrenocorticotropic hormone
ALAN	artificial light at night
ANG	angiotensin
ANP	atrial natriuretic peptide
ANS	autonomic nervous system
ARBs	angiotensin receptor blockers
AT1	angiotensin type-1
AVP	arginine vasopressin
BP	blood pressure
BTCT	bedtime chronotherapy
Ca^{++}	calcium
cAMP	cyclic adenosine monophosphate
CCBs	calcium-channel blockers
cGMP	cyclic guanosine monophosphate
CGRP	calcitonin gene-related peptide
Cl^{-}	chloride
CMTT	conventional morning time therapy
CNS	central nervous system
CO	cardiac output
CRH	corticotropin-releasing hormone
CTS	circadian time structure
CV	cardiovascular
DBP	diastolic blood pressure
EEG	electroencephalography
ET-1	endothelin 1
FMD	flow-mediated endothelium-dependent vasodilatation
GFR	glomerular filtration rate
h	hour
H_2O	water
HOPE	heart outcomes prevention evaluation
HPAA	hypothalamic-pituitary-adrenal axis
HPTA	hypothalamic-pituitary-thyroid axis
HR	hazard ratio
ipRGCs	intrinsically photosensitive retinal ganglion cells
K^{+}	potassium
LURIC	Ludwigshafen risk and cardiovascular health
MAPEC	Monitorización Ambulatoria para Predicción de Eventos cardiovasculares (English: ambulatory blood pressure monitoring for prediction of cardiovascular events)
Na^{+}	sodium
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NO	nitric oxide
NOS	nitric oxide synthase
NREM	non-rapid eye movement
PNS	parasympathetic nervous system
PRA	plasma renin activity
RAAS	renin-angiotensin-aldosterone system
RBF	renal blood flow
REM	rapid eye movement
RORα	retinoid-related orphan receptor alpha
SBP	systolic blood pressure
SCN	suprachiasmatic nuclei
SNS	sympathetic nervous system
SPRINT	systolic blood pressure intervention
TPR	total peripheral resistance
TRH	thyrotropin-releasing hormone
TSH	thyroid stimulating hormone
UV	ultraviolet

circadian rhythms to the BP day/night pattern of diurnally active normotensive and uncomplicated hypertensive human beings.

Circadian rhythms, which in aggregate compose the circadian time structure (CTS), are governed by a master brain oscillator, the paired suprachiasmatic nuclei (SCN) located within the hypothalamus, through a cyclic transcriptional–translational feedback loop of ~24 h duration. In diurnally active mammals, this entails during nighttime darkness activation of *Per1*, *Per2*, *Per3*, *Cry1*, *Cry2*, and *RevErbα* clock-gene transcription, triggered by heteromerization of *Clock* and *Bmal* clock gene products CLOCK and BMAL1, and in the early morning their suppression by nuclear PER and CRY proteins [19–21]. The CTS is hierarchically organized; the SCN regulates peripheral cell, tissue, and organ circadian oscillators of identical mechanism via humoral, endocrine, and neural signals to coherently organize in time virtually all biological processes [19–21]. Because the inherited period of the central and peripheral oscillators differs somewhat from exactly 24.0 h, cyclic external time cues, the most important one being the 24 h light/dark cycle, are required to achieve synchronization of the endogenous CTS. Environmental time information in the form of the onset (sunrise) and offset (sunset) of daylight is sensed by intrinsic non-rod/non-cone ganglion cells of the retinae, i.e., intrinsically photosensitive retinal ganglion cells (ipRGCs), and conveyed via the retinohypothalamic neural pathway first to the SCN and thereafter to the paraventricular nucleus, hindbrain, spinal cord, and superior cervical ganglion neural pathways to β and α receptors within the pineal gland to regulate the circadian rhythm of melatonin synthesis [20,22]. Melatonin plays a major role in biological time-keeping; synthesis and circulation of this short-half-life (~20–40 min) hormone occurs only during nighttime darkness; thus, in humans plasma and tissue melatonin concentration peaks during nocturnal sleep, while it is essentially undetectable during daytime activity [22]. Accordingly, the period of the SCN and subservient peripheral clocks is synchronized, i.e., set and reset from day to day, to 24.0 h, and the phasing (peak and trough) of the rhythms they generate correctly timed to support optimal biological efficiency during daytime wakefulness and rest and repair during nighttime sleep.

Endogenous mechanisms of BP circadian rhythmicity

Wake/sleep rhythm

The wake/sleep cycle, the most evident circadian rhythm of life, is an important endogenous determinant of BP nyctohemeral variation. The wake/sleep cycle, which is controlled by a multitude of basic sensory, motor, autonomic, endocrine, and cerebral 24 h rhythms [23], derives from alternating-in-time dominance of mutually inhibitory actions of arousal/activating systems – cholinergic, serotonergic, and histaminergic nuclear groups of the rostral pons, midbrain, and posterior hypothalamus plus cholinergic neurons of the basal forebrain – and hypnogenic/deactivating systems – medial preoptic-anterior hypothalamus and adjacent basal forebrain, medial thalamus, and medulla, plus pineal gland via melatonergic mechanisms. Phasing of the 24 h rhythms of