Cardiac Clocks and Preclinical Translation

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KEYWORDS

• Circadian • Clocks • Cardiovascular • Heart disease • Circadian rhythm

KEY POINTS

- Circadian rhythms play a crucial role in cardiovascular health.
- Disturbing rhythms causes heart disease and worsens outcomes.
- Translational application of circadian biology to clinical medicine shows enormous potential for directly benefiting patients with cardiovascular disease.

INTRODUCTION

Circadian rhythms are important for healthy cardiovascular physiology. Staying in synchrony with the earth's 24-hour day and night (diurnal) cycle provides benefits to the daily functioning of our cardiovascular system. Conversely, desynchrony with the external environment, for example, through jet lag, shift work, or sleep disorders, has profound adverse effects on our cardiovascular system. Importantly, this has led a flurry of recent investigations with a translational focus, specifically on how circadian biology can be applied to benefit treatment of heart disease. For example, time-of-day therapy (chronotherapy) with angiotensin-converting enzyme inhibitors (ACEi) benefits treatment in experimental murine models of heart disease. Moreover, clinical cardiology benefits from chronotherapy and recent successes include evening administration of antihypertensives for non-dippers, aspirin at night to reduce morning risk of myocardial infarction (MI), nocturnal hemodialysis, and nocturnal continuous positive airway pressure (CPAP) for patients with obstructive sleep apnea (OSA). Evidence is also emerging that short-term circadian and sleep disruption, as occurs in intensive care units (ICUs), may hamper recovery after MI. Maintaining the diurnal environment and patients biological rhythms is a promising nonpharmaceutic approach to reduce scar expansion and improve outcomes after MI. Finally, recent studies give rise to 3 new frontiers for translational research: (1) applications to benefit cardiovascular disease in the aging population; (2) new understanding of circadian mitophagy in regulating cardiac bioenergetics; and (3) links between the circadian clock mechanism and cognitive impairment or depression in heart disease. Recognizing the fundamental role that the circadian mechanism plays in cardiovascular health and disease is leading to new translational applications for clinical cardiology.

CIRCADIAN RHYTHMS IN THE CARDIOVASCULAR SYSTEM

This section provides an overview of the molecular circadian mechanism, and its role in regulating

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healthy cardiovascular physiology as well as in the in the timing of onset of adverse cardiovascular events.

Overview of the Circadian Mechanism in the Heart

Molecular circadian clocks are present in all our cells, including cardiomyocytes.[1–4] This mechanism enables us to entrain to environmental cues and anticipate the differing physiology demands of our everyday events, including those of the cardiovascular system. The circadian mechanism at a most basic level is a transcriptional-translational loop that cycles once every 24 hours to keep cellular time, and it is illustrated in **Fig. 1** (there are excellent reviews[5,6]). Briefly, the positive arm (see **Fig. 1**, *green*) consists of a heterodimeric pairing of CLOCK and BMAL1 proteins, which bind to promoter E-boxes to induce expression of the repressors PERIOD and CRYPTOCHROME. In the negative arm (see **Fig. 1**, *purple*), the repressors PER and CRY are phosphorylated by CASEIN KINASE, leading to inhibition of their transcription. In addition to regulating 24-hour diurnal clock cycles, this mechanism also controls diurnal patterns of tissue-specific output genes, those which regulate cardiac structure and function on a daily basis.[7,8] Collectively, transcription of approximately 10% of the genes[1,2,8–11] and translation of approximately 10% of the proteins[12,13] in the heart, as well as vasculature[8,14,15] and other tissues,[16,17] are under circadian control.

Circadian Rhythms and Healthy Cardiovascular Physiology

The output of the circadian mechanism is observed as diurnal physiologic rhythms, many crucial to the cardiovascular system. For example, there is daily cyclic variation in heart rate (HR), which is highest in the day and lowest during the night.[18] Blood pressure (BP) also displays a daily rhythm that is highest in the morning, falls progressively throughout the day and early evening, and then reaches a nadir around 3:00 AM.[19] Diurnal rhythms in BP are considered especially important for cardiovascular health, because clinically, humans with 24-hour BP profiles that do not follow the normal diurnal pattern are at a higher risk of heart disease. That is, most people have a nocturnal dip in BP of approximately 10% as compared with the daytime.[19] However, hypertensive nondippers (patients who do not experience the anticipated drop in BP at night),[20] or patients without hypertension but still a diminished nocturnal decline in BP,[21] exhibit an increased risk of heart disease. These diurnal rhythms in HR and BP parallel the sympathetic and parasympathetic biases of our autonomic nervous system,[22,23] and they are endogenously generated.[24–26]

Circadian Rhythms in the Timing of Onset of Adverse Cardiovascular Events

Rhythms are important not only for healthy cardiovascular physiology but also for the timing of onset

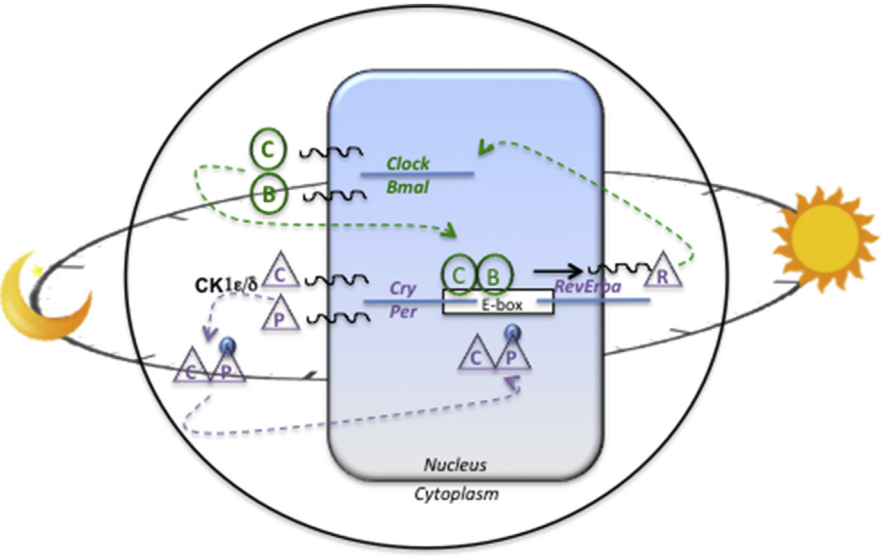

Fig. 1. The molecular circadian clock mechanism cycles in virtually all cells, including cardiomyocytes, and plays a direct role in regulating the daily output of thousands of genes, proteins, and metabolites. These in turn play key roles in regulating the structure and function of the healthy heart and contribute to cardiac remodeling and the pathophysiology of heart disease.