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Review

Consequences of Circadian and Sleep Disturbances for the Cardiovascular System

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ABSTRACT

Circadian rhythms play a crucial role in our cardiovascular system. Importantly, there has been a recent flurry of clinical and experimental studies revealing the profound adverse consequences of disturbing these rhythms on the cardiovascular system. For example, circadian disturbance worsens outcome after myocardial infarction with implications for patients in acute care settings. Moreover, disturbing rhythms exacerbates cardiac remodelling in heart disease models. Also, circadian dyssynchrony is a causal factor in the pathogenesis of heart disease. These discoveries have profound implications for the cardiovascular health of shift workers, individuals with circadian and sleep disorders, or anyone subjected to the 24/7 demands of society. Moreover, these studies give rise to 2 new frontiers for translational research: (1) circadian rhythms and the cardiac sarcomere, which sheds new light on our understanding of myofilament structure, signalling, and electrophysiology; and (2) knowledge translation, which includes biomarker discovery (chronobiomarkers), timing of therapies (chronotherapy), and other new promising approaches to improve the management and treatment of cardiovascular disease. Reconsidering circadian rhythms in the clinical setting benefits repair mechanisms, and offers new promise for patients.

RÉSUMÉ

Les rythmes circadiens jouent un rôle crucial dans notre système cardiovasculaire. Notamment, une récente avalanche d'études cliniques et expérimentales révélant les conséquences indésirables profondes de la perturbation de ces rythmes sur le système cardiovasculaire ont été réalisées. Par exemple, la perturbation des rythmes circadiens détériore les résultats cliniques après l'infarctus du myocarde des patients en soins de phase aiguë. De plus, la perturbation des rythmes exacerbe le processus de remodelage cardiaque des modèles de cardiopathie. Aussi, la dyssynchronie circadienne est un facteur causal dans la pathogenèse de la cardiopathie. Ces découvertes ont de profondes conséquences sur la santé cardiovasculaire des travailleurs de quart, des individus ayant des troubles du rythme circadien et du sommeil, ou de tout individu soumis tous les jours 24 heures sur 24 aux exigences de la société. En outre, ces études mettent en exergue 2 nouvelles frontières de la recherche translationnelle : 1) les rythmes circadiens et le sarcomère cardiaque, lequel jette un nouvel éclairage sur notre compréhension de la structure des myofilaments, de la signalisation et de l'électrophysiologie; 2) l'application des connaissances, qui comprend la découverte des biomarqueurs (chronobiomarqueurs), le meilleur moment des thérapies (chronothérapie) et d'autres nouvelles approches prometteuses pour améliorer la prise en charge et le traitement de la maladie cardiovasculaire. La reconsidération des rythmes circadiens en milieu clinique favorise les mécanismes de réparation et s'avère prometteuse pour les patients.

Jürgen Aschoff was a physician, scientist, and cofounder of the field of circadian biology. He introduced the notion that day and night (diurnal) rhythms in physiology are a fundamental feature in most living organisms including humans.[1] We now know that rhythms are regulated by the circadian system, by orchestration in the hypothalamic suprachiasmatic nucleus, and through neural and hormonal outputs to all organs including the heart (Fig. 1A).[2-7] Mechanistically, an exquisite underlying cellular clock mechanism has been identified, which controls molecular rhythms in virtually all cells including cardiomyocytes (Fig. 1B).[8,9] Over the past 5 decades numerous clinical and experimental studies have revealed a crucial role for the circadian system in regulating healthy physiology. Most recently, studies by our group and others have shed light on the profound adverse health consequences of circadian disturbances, underlying cardiovascular, cancer, metabolic, respiratory, psychiatric, and other disorders.[6,10-15] In this review we focus on the consequences of circadian disturbances on the pathogenesis and pathophysiology of heart disease.

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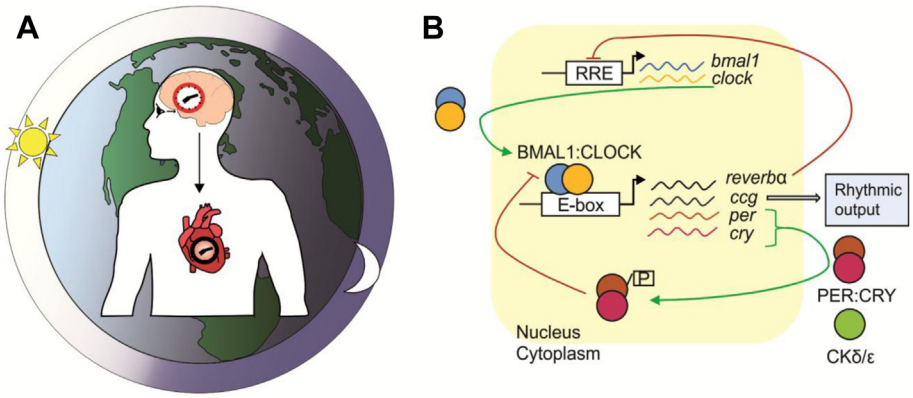

Figure 1. Circadian rhythms. (**A**) Schematic representation of the circadian hierarchical oscillator model and the outputs that influence cardiovascular processes. The suprachiasmatic nucleus in the hypothalamus synchronizes peripheral organ clocks, including the heart, to entrain to the 24-hour light-dark environment. (**B**) The molecular clock mechanism keeps 24-hour time via transcription-translation feedback loops. The primary negative feedback loop consists of response element (RRE) driven Brain and Muscle ARNT Like 1: Circadian Locomotor Cycles Kaput (BMAL1:CLOCK), which leads to Period (PER) and Cryptochrome (CRY) production, PER:CRY phosphorylation by Casein Kinase 1 δ/ε (CKδ/ε), and PER:CRY self-repression. BMAL1:CLOCK also drives Nuclear Receptor Subfamily 1, Group D, Member 1 (REV-ERBα) expression, which represses BMAL1. This mechanism regulates expression of clock-controlled genes (ccg) which regulate rhythmic biological processes.

Circadian Biology and Normal Cardiovascular Physiology

Circadian rhythms in heart rate and blood pressure

Circadian rhythms are important for daily cyclic variation in mammalian physiology, for example our heart rate (HR) is highest during wake and lowest during sleep.[16] Blood pressure (BP) also displays a daily rhythm, indeed, Floras and colleagues documented for the first time the remarkable BP surge that occurs at the time of waking and morning activity.[17] BP is highest in the morning and decreases progressively (approximately 10%) to reach a nadir during sleep.[18] These rhythms are consistent with the diurnal biases of our autonomic nervous system, which oscillate over 24-hour periods.[19] Thus our cardiovascular physiology exhibits striking time of day-dependent oscillations. Remarkably, diurnal variations in HR and cardiac contractility observed in vivo still persist ex vivo, for example, when rodent hearts are perfused on a Langendorff apparatus.[13,20] Thus it is not just the neurohormonal axes that contribute to time of day cardiac physiology, but also the intrinsic circadian properties of the heart. Over the past decade this has given rise to numerous experimental studies that show a direct role for the circadian mechanism on our daily cardiovascular physiology, as is demonstrated experimentally in rats[21-24] and mice.[13,25,26]

Daily timing of onset of adverse cardiovascular events

Adverse cardiovascular events are a leading cause of death worldwide and do not occur at random times throughout the day. An early morning peak of acute myocardial infarction (MI) was first reported in 1985,[27] and in the decades since, despite changes in lifestyle and advances in medicine, the pattern of morning excess of MI persists.[28-33] A diurnal pattern also occurs for infarct size,[34-36] stroke,[37] angina,[38] ventricular tachyarrhythmia,[39-41] defibrillation energy requirements,[42] ventricular refractoriness,[43] and sudden cardiac death.[44-46] Physiologically, sympathovagal balance is thought to play a causal role, because patients with autonomic nervous system dysfunction do not exhibit the early morning peak in timing of onset of MI.[47-49] Several studies have highlighted additional factors, many under circadian control, which increase the risk of adverse cardiovascular events, including diurnal rhythms in platelet activity,[50-53] thrombosis or thrombolysis,[54-56] and endothelial function.[57] Mechanistically, a direct role for the circadian mechanism underlying time of day dependence has been demonstrated in humans[52,58] and animal models.[34,59-61]

Diurnal variations in cardiomyocyte metabolism

As described, cardiac function displays a time of day effect, driven in part by the sympathetic environment and the neurohormonal milieu. However, at the myocyte level, there is considerable new evidence that intrinsic cellular properties also occur in a circadian manner, as has been exquisitely detailed in studies by Young and colleagues. To summarize, this is especially evident from the ex vivo perfused rat or mouse heart models, which demonstrate persistence of time of day variations in cardiac metabolism, even in the absence of neural and hormonal cues.[20,62,63] Day/night variations in cardiac metabolism allow the heart to switch between different substrates (mainly glucose and fatty acids) for energy sources depending on availability over the course of 24-hour periods.[64,65] These intrinsic cardiomyocyte processes are facilitated in part by the cardiomyocyte-specific circadian clock mechanism.[13,66] This circadian mechanism regulates messenger RNA (mRNA) and protein expression of key metabolic factors in cardiomyocytes as described herein, thus controlling cellular processes in a time of day-dependent manner.

Circadian genomics

The heart is genetically a different organ in the day vs the night. The first large-scale microarray study to demonstrate this revealed that approximately 8% of genes are rhythmic in murine hearts under circadian (constant dark) conditions.[67]