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Review article

Implications of disturbances in circadian rhythms for cardiovascular health: A new frontier in free radical biology

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ABSTRACT

Cell autonomous circadian "clock" mechanisms are present in virtually every organ, and generate daily rhythms that are important for normal physiology. This is especially relevant to the cardiovascular system, for example the circadian mechanism orchestrates rhythms in heart rate, blood pressure, cardiac contractility, metabolism, gene and protein abundance over the 24-h day and night cycles. Conversely, disturbing circadian rhythms (e.g. via shift work, sleep disorders) increases cardiovascular disease risk, and exacerbates cardiac remodelling and worsens outcome.

Notably, reactive oxygen species (ROS) are important contributors to heart disease, especially the pathophysiologic damage that occurs after myocardial infarction (MI, heart attack). However, little is known about how the circadian mechanism, or rhythm desynchrony, is involved in these key pathologic stress responses.

This review summarizes the current knowledge on circadian rhythms in the cardiovascular system, and the implications of rhythm disturbances for cardiovascular health. Furthermore, we highlight how free radical biology coincides with the pathogenesis of myocardial repair and remodelling after MI, and indicate a role for the circadian system in the oxidative stress pathways in the heart and brain after MI. This fusion of circadian biology with cardiac oxidative stress pathways is novel, and offers enormous potential for improving our understanding and treatment of heart disease.

1. Introduction

Circadian rhythms are our internal day/night cycles of behaviour and physiology. They enable us to coordinate our biology with the external environment - to adapt to light and dark, activity and rest, and wake and sleep (reviewed in [1,2]). Circadian rhythms are endogenously driven by a cellular mechanism, which is a transcription-translation feedback loop with an approximately 24-h duration that cycles in all our cells including those of the cardiovascular system [3–7]. A region of the hypothalamus, termed the suprachiasmatic nucleus (SCN), orchestrates the cellular circadian mechanism in the tissues throughout our body, and helps to maintain healthy body physiology (reviewed in [8,9]). Indeed, it is increasingly recognized that intact circadian rhythms play an essential role in maintaining cardiovascular health, well-being, and recovery from heart disease (reviewed in [9–15]). Conversely, disturbing rhythms is associated with an increased risk of heart disease, adverse cardiovascular events, and worse outcomes (reviewed in [9–13,15–17]). Circadian rhythm disturbance is especially relevant in modern society, where we often experience desynchrony due to shift work, sleep disorders, jet-lag, school and work schedules, and the ubiquitous presence of 24/7 electrical lighting.

In this review we discuss circadian rhythms relevant to the cardiovascular system. We provide an overview of the current literature with regard to healthy cardiovascular physiology, and what happens when we disturb rhythms. This includes clinical studies relevant to humans, as well as experimental rodent models that help to define the underlying mechanisms. We highlight especially how disturbing rhythms may pertain to the free radical biology pathways, contributing to the pathophysiology or treatment of heart disease. This is an entirely new frontier for investigation, and increased understanding of such mechanisms will lead to new avenues for applying circadian biology to benefit patients clinically.

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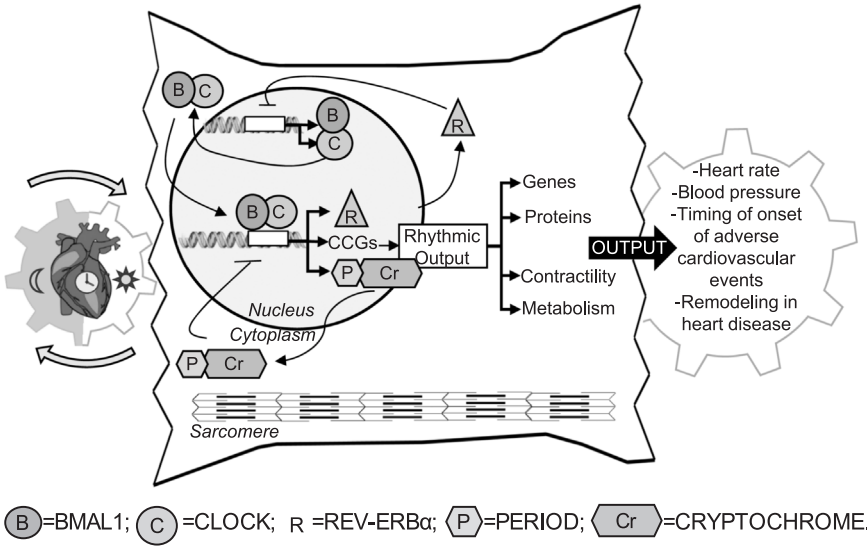

Fig. 1. The molecular circadian mechanism. The circadian clock mechanism in cardiomyocytes regulates the 24-h day/night expression of genes and proteins, cardiac contractility and metabolism. We observe the output of the clock mechanism as daily rhythms important for normal cardiovascular physiology, including heart rate (HR) and blood pressure (BP) which peak in the day and trough at night. These rhythms also play a role in the pathogenesis and pathophysiology of heart disease

2. Circadian rhythms in normal cardiovascular physiology

Life on earth is subjected to 24 h day and night cycles. The circadian system has evolved to allow our physiology to be synchronous with this cycle – humans adapt to be awake during the day and sleep at night. As shown in Fig. 1, the circadian mechanism undergoes rhythmic daily cycling in all our cells, including the cardiomyocytes [3,18]. This regulates the rhythmic output of cardiac genes [3,7] and proteins [19–22], cardiac contractility [19,22–24], and metabolism [9,25]. Ultimately, we observe the output of this cellular mechanism as daily physiologic and behavioural rhythms, many of which are crucial to the cardiovascular system [9,10]. For example, our heart rate [26] and blood pressure [27,28] increase in the day and decrease at night. These normal cardiovascular rhythms help to prepare individuals for the physiological demands of rigorous activity during the day, and are associated with rest and renewal at night (reviewed in [10]). Our endocrine hormones cycle as well, including many relevant to the cardiovascular system. For example, the catecholamines epinephrine and norepinephrine peak in the day and trough at night in healthy individuals [29,30], paralleling the sympathetic and parasympathetic biases of our autonomic nervous system [31,32]. Moreover, circulating levels of innate immune cells and cytokines [30,33–38], clotting factors [30,39], and other classic biomarkers of normal cardiovascular physiology show a similar diurnal pattern [3,19,21,24,25,40]. There is also a morning rise in cortisol and nighttime peak in melatonin; these biomarkers are indicative of central circadian efficiency and diurnal homeostasis [41–43]. Collectively these daily rhythms are beneficial for helping to maintain normal cardiovascular function in healthy people.

3. Circadian rhythms and timing of onset of acute cardiovascular events

Daily rhythmicity is important for a healthy cardiovascular system, yet it also creates a circadian-regulated window of vulnerability that underlies heart disease. The risks for myocardial infarction (MI), sudden cardiac death, ventricular arrhythmias and stroke are greater in the early morning hours as compared to any other time of day or night. There are excellent reviews on the diurnal timing of acute cardiovascular events in humans [9,44,45]. The basic notion is that acute cardiovascular events do not occur randomly throughout the day, but are precipitated in part by circadian regulated factors that create a prothrombotic and/or pro-ischemic state in the early daytime hours [10,11,46,47]. For example, our morning rise in blood pressure is concurrent with increased cardiac output, which has implications for the rupturing of plaques. Similarly, catecholamines surge around wake time and act on the vasculature to increase vasoconstriction and intra-arterial pressure, further precipitating the likelihood of plaque erosion or rupture. There is also greater platelet reactivity (and thus aggregability) and decreased fibrinolysis in the morning, which increases the risk of more aggressive thrombosis or clot formation. Collectively, these circadian regulated factors conspire to increase the likelihood of adverse cardiovascular events during the vulnerable early morning period.

4. Implications of disturbances of circadian rhythms for heart disease in humans

Many individuals experience disturbances in circadian rhythms as a consequence of working in modern society, and this can have profound implications for cardiovascular disease in humans. Approximately 28% of the western workforce operates outside of conventional daytime hours, according to Statistics Canada [48]. Moreover, shift work is considered a risk factor for coronary heart disease, sudden cardiac death, as well as other clinical pathologies, according to the World Health Organization [49]. Mechanistically, frequent shifting of wake and sleep times causes our circadian-controlled central clock (e.g. cortisol and melatonin) [50,51] and peripheral physiology (e.g. blood pressure [52], endocrine hormones [42], catecholamines and other measures of sympathetic tone [43,53], and genes and proteins [23,40,54,55]) to fall out of sync. Many of these factors are crucial for the cardiovascular system such that our internal circadian physiology becomes misaligned with the external environment, and has implications for our health [17]. For instance, shift workers will eat during night shifts, which is not the conventional time for postprandial processes and normal energy metabolism and expenditure [56]. Atypical work shifts leading to fatigue are an obvious factor contributing to reduced performance efficiency and safety concerns [57]. However, even beyond the acute detrimental effects of shift work, chronic desynchrony via long term atypical work schedules is believed to directly and adversely impact our health, and especially our cardiovascular system (reviewed in [9–13]). Thus collectively, these studies demonstrate the crucial relationship between circadian rhythm disturbance and implications of disturbances on the cardiovascular system.

5. Implications of disturbances of circadian rhythms in experimental murine models of heart disease

Rhythm disturbance has profound implications for the cardiovascular system, as noted above. Experimental studies then help to define a direct link between the circadian mechanism and heart health and