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Review Article

An overview of the emerging interface between cardiac metabolism, redox biology and the circadian clock

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ABSTRACT

At various biological levels, mammals must integrate with 24-hr rhythms in their environment. Daily fluctuations in stimuli/stressors of cardiac metabolism and oxidation-reduction (redox) status have been reported over the course of the day. It is therefore not surprising that the heart exhibits dramatic oscillations in various cellular processes over the course of the day, including transcription, translation, ion homeostasis, metabolism, and redox signaling. This temporal partitioning of cardiac processes is governed by a complex interplay between intracellular (e.g., circadian clocks) and extracellular (e.g., neurohumoral factors) influences, thus ensuring appropriate responses to daily stimuli/stresses. The purpose of the current article is to review knowledge regarding control of metabolism and redox biology in the heart over the course of the day, and to highlight whether disruption of these daily rhythms contribute towards cardiac dysfunction observed in various disease states.

1. Introduction

Cardiac metabolism encompasses a highly dynamic array of interlinked pathways designed to meet both the energetic demands of the heart, and provide precursor molecules essential for critical processes as diverse as the synthesis of cellular constituents to signal transduction. Metabolism must be tightly controlled, yet remain plastic, thereby affording an ability to rapidly shift flux between distinct pathways in response to environmental perturbations while meeting energy demands and other biological processes. This is achieved through regulation at both the systemic and organ levels. In this review, we will focus predominantly on the heart to illustrate how circadian biology is integrated with metabolism and the role redox sensitive pathways play in this process. The heart is responsive to the physiological demands of the organism, which is orchestrated by changes in a range of signaling molecules that fluctuate secondarily to diet, physical demands and numerous stimuli/stresses.

Over the last decade our understanding of how reduction or oxidation (redox processes) of proteins can contribute to both physiology and pathology has undergone a paradigm shift. Previously, the field of free radical biology was dominated by the “oxidative stress paradigm”. This has been a popular and straightforward concept that promotes the central idea that there is a balance between free radicals or oxidants [commonly called reactive oxygen species (ROS) or reactive species] with antioxidants in normal physiology [1,2]. Pathology then occurs when reactive species are produced in excess of the endogenous antioxidants, and this leads to indiscriminate damage to cellular macromolecules (proteins, lipids, and DNA) and kills cells [3]. This led to the postulate that ROS are bad and therefore any associated pathologies can be reversed by the appropriate application of antioxidants. Unfortunately, this model does not effectively include the robust literature, which has shown that ROS and nitric oxide (NO) can act as signaling molecules and that the over-expression of endogenous antioxidant enzymes can be toxic to the cell [4]. In this review we will use the general term ROS unless the studies being discussed have identified specific reduction products of oxygen [5]. To address these issues we, and others, have promoted the “redox biology” paradigm in which antioxidants play the primary role of modulating the complex networks controlling cell signaling and metabolism, such that pathology results from loss of control over specific intracellular domains [6,7]. In this review, we use the term “redox” to refer to oxidative or reductive processes that have the potential to control cellular function. In some cases these redox events can be specifically defined at redox sensitive amino acids, such as cysteine, but in others we do not have

Abbreviations: NOS, nitric oxide synthase; NO, Nitric Oxide; NOX, NADPH oxidase; LC3, Microtubule associated protein light chain 3; ROS, reactive oxygen species; NRF2, nuclear factor (erythroid-derived 2)-like 2; KEAP1, kelch-like ECH-associated protein 1; PPP, pentose phosphate pathway

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this level of resolution. In writing this review it became clear, that apart from some pioneering studies, remarkably little is known about the interface between circadian and redox biology, particularly in the heart. Wherever possible, information is provided in a manner that allows the reader to have a more complete picture of the field, including its limitations and opportunities.

It is now becoming clear that cardiac metabolism is aligned with time of day, through both extrinsic (e.g., neurohumoral factors) and intrinsic (e.g., circadian clock) influences [8,9]. During various disease states (including aging), metabolic plasticity is often attenuated/abolished [10,11], and this is frequently associated with loss of control of redox homeostasis and progression of cardiac pathologies. Metabolism and redox biology are closely interlinked, and like metabolism, the redox status of specific regions in the cell are maintained within specific set points (termed redox tone), through adaptive regulation of the redox network [6,7,12–17]. As with cardiac metabolism, redox biology exhibits a time of day dependence, supporting the notion that the integration of metabolic and redox signaling with biological clocks is essential for normal physiology [18–21]. Furthermore, the incidence of adverse cardiovascular events (e.g., myocardial infarction, sudden cardiac death) is time-of-day-dependent, occurring more frequently in the early morning hours [22]; these rhythms occur in parallel with fluctuations in cardiac metabolism and redox tone. The purpose of the current article is to review knowledge regarding control of metabolism and redox biology in the heart over the course of the day, and to highlight whether disruption of these daily rhythms contribute towards cardiac dysfunction observed in various disease states.

2. Rhythms in cardiac metabolism

A great deal of information has accumulated regarding circadian control of metabolism. This section we will use the research literature in the heart, and whenever possible, will attempt to highlight potential links with redox biology (which will be developed further in subsequent sections). Over the course of the day, the myocardium exhibits profound metabolic plasticity at multiple levels, corresponding with time of day-dependent fluctuations in energetic demand and nutrient availability [23]. This is illustrated by physiological changes in myocardial glucose utilization over the course of the day. It has been established that elevation of workload and/or insulin levels rapidly promotes glucose utilization of the heart [24,25]. It is therefore not surprising that during the awake period, a time at which physical activity and food consumption are increased, myocardial glucose utilization has been reported to be increased in both the rat and mouse heart [26–28]. This is observed at the levels of both non-oxidative (e.g., glycolysis, glycogen synthesis) and oxidative (i.e., full catabolism to CO_2) glucose disposal. For example, myocardial glucose oxidation is doubled during the active period, relative to the sleep period [27].

Evidence exists in support of the concept that additional glucose metabolism pathways may be under circadian control. One example includes the hexosamine biosynthetic pathway, which utilizes the glycolytic intermediate fructose 6-phosphate via the glutamine:fructose 6-phosphate amidotransferase reaction, ultimately resulting in post-translational modification of proteins, through O-GlcNAcylation [29]. Importantly, flux through the hexosamine biosynthetic pathway is augmented in the heart during the active period, and is associated with increased protein O-GlcNAcylation at this time [27]. Interestingly, the O-GlcNAc pathway is also responsive to increased oxidative stress and offers a potential mechanistic link between redox regulated pathways and metabolism [6,30]. Glucose dependent metabolism is also essential for providing substrates for the pentose phosphate pathway (PPP), generating NADPH as the key reducing equivalent for maintaining thiol redox status and the controlled generation of ROS or NO through cell signaling. Interestingly, in cell models it has been shown that time dependent oscillations in the PPP result in changes in the peroxiredoxin redox state and the regulator of redox homeostasis, Nrf2 (nuclear factor (erythroid-derived 2)-like 2) [18–20]. Whether PPP flux oscillates over the course of the day in the heart (the topic of the current review article) is currently unknown.

Relative to glucose oxidation, the oxidation of fatty acids by the heart exhibits a minimal time-of-day-dependence, likely reflecting the fact that fatty acids serve an important role in basal cardiac contraction (as opposed to meeting energetic demands during elevated workload) [28,31]. In contrast, triglyceride synthesis (and phospholipid synthesis, to a lesser extent) exhibits a marked daily fluctuation (more than 3-fold), peaking towards the end of the active period in the mouse heart [31]. Moreover, the transcriptional responsiveness of the heart to fatty acids also exhibits a time-of-day-dependence, with greatest induction of fatty acid responsive genes (many of which promote fatty acid oxidation) during the active period (particularly at the beginning of the active period) [32]. Such observations have led to the hypothesis that prolongation of the sleep phase fast into the active period, when, for example, the animal in the wild is unsuccessful in its forage for food, allows the myocardium to rapidly increase reliance on fatty acids as a fuel (which are abundant due to continued lipolysis), while the forage for food continues. Moreover, once successful in its forage for food, increased triglyceride synthesis towards the end of the active period will likely provide an endogenous fuel source for the myocardium during the upcoming sleep period. Promotion of phospholipid synthesis at the beginning of the sleep phase may be important for replacement of damaged (e.g., oxidized) phospholipids (a concept that will be expanded upon below).

The awake-to-sleep transition has emerged recently as an important period of growth and repair of the myocardium. Similar to increased phospholipid synthesis, protein synthesis has been reported to be increased at this time, both in vivo and *ex vivo* [33]. Consistent with

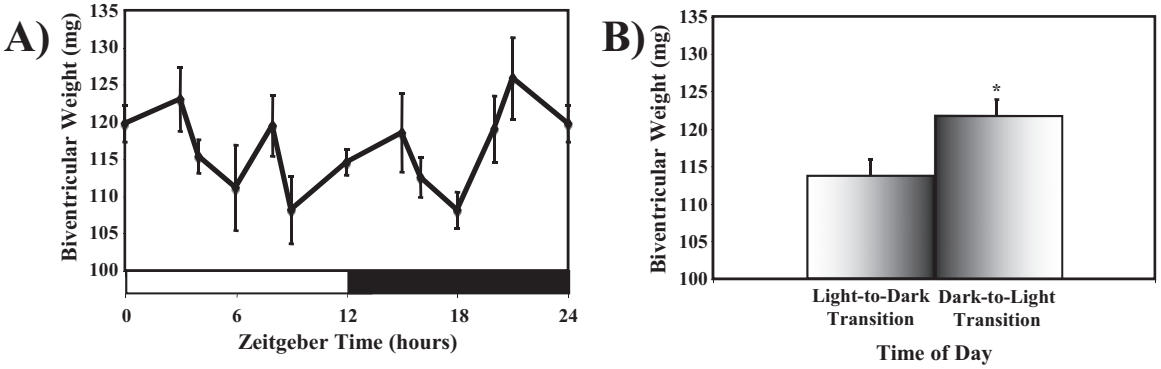

Fig. 1. Time-of-day-dependent fluctuations in biventricular weight of the mouse heart. A: Assimilated data from McGinnis et al. and Brewer et al. shows time-of-day-dependent fluctuations in biventricular weight (mg). B: Murine biventricular weight is 6.9% higher at the awake-to-sleep (dark-to-light; average of ventricles collected at ZT21, ZT24/0, and ZT3; n = 28) transition compared to the sleep-to-awake (light-to-dark; average of ventricles collected at ZT9, ZT12, and ZT15; n = 26) transition.