



Circadian rhythms and cardiovascular disease

Danielle Feuvray
University of Paris-Sud 11 and UMR CNRS 8162, France

Correspondence: Professor Danielle Feuvray, University Paris-Sud 11 and CNRS UMR 8162, Marie Lannelongue Hospital, 92350 Le Plessis Robinson, France.
E-mail: danielle.feuvray@u-psud.fr

Circadian rhythms are daily, approximately 24-hour oscillations in physiology and behavior such as food consumption, blood pressure, and metabolism. These rhythms are believed to give an adaptive advantage by allowing an organism to anticipate changes in the environment and regulate its physiology accordingly. It is well recognized that aspects of both cardiovascular physiology and the clinical manifestation of cardiovascular disease display diurnal variations. The central loci of the mammalian clock are two small clusters of hypothalamic neurons called the suprachiasmatic nuclei (SCN), which constitute the master pacemaker that orchestrates rhythmic patterns of behavior and physiology throughout the organism. For many years, neurons of the SCN were believed to contain the unique clock controlling circadian rhythmicity of peripheral tissues via neural and humoral signals. Surprisingly, the cloning and characterization of mammalian clock genes have revealed that most tissues in the body also contain autonomous circadian clocks* that are necessary for the rhythmic expression of clock output genes. These peripheral oscillators, which share many of their molecular components with the master oscillator, can also be distinguished by the expression of specific transcription factors. The molecular oscillator is composed of interlocking positive and negative transcriptional and translational feedback loops that drive the circadian expression of genes.

In this issue of *Heart and Metabolism*, the Basic Article by Drs Tsai and Young offers a detailed review regarding diurnal variations in myocardial cell metabolism. A striking example is given by the modulation in the responsiveness of the heart to fatty acids, the primary fuel source for the healthy myocardium. Elegant studies in rodent hearts have shown that diurnal variations in the responsiveness of the heart to fatty acids are mediated by the cardiomyocyte circadian clock. Variations are preserved in single cells *ex vivo*, provided that the circadian clock within the cardiomyocyte is fully functional. Interestingly, the rhythmic expression of genes regulated by the circadian clock is disturbed in various pathological states. The New Therapeutic Approaches article by Drs Duez and Staels points out that recent data demonstrate, not only that the expression of certain nuclear receptors is driven by the circadian clock, but also that they participate in the circadian control of metabolism. In particular, the nuclear receptor Rev-erb α is involved in the regulation of the core clock machinery and, consequently, may play a central part in orchestrating the temporal coordination of metabolism in several cell types. The recent identification of natural (heme) and synthetic ligands for Rev-erb α suggests that it may represent a potential target for the treatment of metabolic diseases that are related to disturbance of circadian rhythms. Whether Rev-erb α is expressed in a circadian manner in the heart, cells of

Editorial

Danielle Feuvray

the vascular wall, or cardiac myocytes remains to be elucidated.

In the Main Clinical Article of this issue of *Heart and Metabolism*, Dr Dominguez-Rodriguez and colleagues give a superb overview of the available evidence linking disruption of circadian rhythms to cardiovascular disease. There is indeed a universal appreciation of the presence of diurnal variations in the response of the cardiovascular system in both physiological and pathophysiological circumstances. Serious adverse cardiovascular events appear to be conditioned by time of day. Therefore biological responses, which are under the control of the molecular clock (within both cardiac myocytes and vascular smooth muscle cells), may interact with environmental cues to influence the clinical manifestation of cardiovascular disease.

The Refresher Corner by Drs Reiter and Tan points out that melatonin*, a hormone produced mainly in the pineal gland, may have a protective role in reducing cardiac ischemia-reperfusion injury, as shown in experimental models. Melatonin, an endogenous

signal of darkness, is an important component of the body's internal time-keeping system. This is subtly illustrated by the jet-lag syndrome described in the Case Report by Dr Jackson. Melatonin regulates major physiological processes. Reiter and Tan also underline that, in addition to its relevant antioxidant activity, melatonin exerts many of its physiological actions by interacting with specific membrane receptors. There are circadian variations in the expression of the melatonin receptor and, possibly, signal transduction pathways in various organs, including the heart. Further investigations are needed to clarify the potential importance of the use of melatonin in situations of oxidative damage to the heart in humans.

This issue of *Heart and Metabolism* provides a contemporary description of various aspects by which circadian rhythms may control the coordination of metabolic processes. It also highlights that disturbances of the circadian clock may predispose or lead to metabolic disorders and therefore influence the phenotype of cardiovascular disease.

*See glossary for definition of these terms.