

Circadian Clocks

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Preface

The human body functions as a 24-h machine: remarkably, this machine keeps going with a *circa* 24-h rhythm in sleeping and waking, in physiologies such as blood pressure and cortisol production, in cognitive functions, and indeed also in expression of circa 10–20 % of the genome in any given cell. The circadian (from the Latin “*circa diem*” or about a day) clock controls all of these processes with a molecular mechanism that is pervasive, as we now know that essentially every cell of our body is oscillating. Furthermore, our cells apparently utilize a circadian clock mechanism with a similar molecular makeup. The recent years have witnessed an enormous progress in our understanding of the mechanistic and genetic basis of this regulation, which we have tried to highlight in this volume.

The circadian clock is relevant for health—clock gene mutants show reduced fitness, increased cancer susceptibility and metabolic diseases. In addition, drug efficacy and toxicity often vary with time of day with huge implications for therapeutic strategies. The intention of this book is to provide the reader with a comprehensive and contemporary overview about the molecular, cellular and system-wide principles of circadian clock regulation. In keeping with the focus of the *Handbook of Experimental Pharmacology* series, emphasis is placed on methods as well as the importance of circadian clocks for the timing of therapeutic interventions. Despite the decades-old practice of administration of cortisol on the morning, chronopharmacology and chronotherapy are still mostly at an experimental level. Thus, knowledge about the widespread impact of circadian clocks should be invaluable for a broad readership not only in basic science but also in translational and clinical medicine.

This book contains four topical sections. Part I is devoted to describing our current knowledge about the molecular and cellular bases of circadian clocks. In the first chapter, the readers learn about clock genes and the intracellular genetic network that generates ~24-h rhythms on the molecular level. The second chapter focuses on how the circadian clock is using epigenetic mechanisms to regulate the circadian expression of as many as 10 % of cellular transcripts. The following two chapters focus on the hierarchy of mammalian circadian organization: the clock in the brain is the master pacemaker, often controlling daily timing in peripheral

tissues. The mechanisms of these synchronization processes within tissues and organisms are discussed.

Part II of the book is devoted to describing how and what is controlled by the circadian clock. The general term for this is *outputs* of the clock. Here, we will cover sleep, metabolism, hormone levels and mood-related behaviors that are especially relevant to pharmacology. In recent years, the reciprocal control of metabolic processes and the circadian system emerged, which is the focus of the first chapter of this part. This connection has been elucidated both on a molecular basis and also in epidemiological studies. Several common themes will emerge including the feedbacks between clocks and the clock output systems as well as the balance between local and tissue-specific clocks and the system-wide control of circadian functions. Concerning human behavior, there is nothing more disparate than the states of sleep and wakefulness; the reader will learn that the timing of these states is profoundly governed by the circadian clocks and its associated genes (see also Part III, Roenneberg et al.). Single point mutations in clock genes can dramatically alter sleep behavior. Disruption of temporal organization—clock gene mutations or shift work—can lead to health problems and behavioral disorders related to mood alterations. The last chapter in this section discusses these connections and possible *pharmacological* interventions such as light or lithium therapy.

The aim of Part III is to discuss the implications of a circadian system for pharmacology. The first chapter reviews studies from the past several decades that describe daily changes in drug absorption, distribution, metabolism, and excretion. In addition, drug efficacy is controlled by the circadian system due to daily changes in the levels and functionality of many drug targets. The second chapter exemplifies these principles for anticancer therapy, where chronotherapy is relatively advanced. This may be based on the fact that cancer cells have less synchronized circadian clocks. Modulating or strengthening the molecular clock by pharmacological intervention is a strategy that is addressed in one of the contributions in this section. High-throughput screening approaches for small molecules that are capable of pharmacological modulation of the molecular clock are described—this may develop into a valuable approach for both scientific and therapeutic purposes. The last chapter in this section focuses on the role of light for the synchronization of the human clock to our environment (entrainment). Light is the primary synchronizer (*zeitgeber*), and novel light-sensitive cells in the retina mediate entrainment, which is conceptually and epidemiologically analyzed. In shift work, as well as in everyday working life, the dissociation of internal and external time leads to health problems, suggesting the need for intervention strategies that use light as though it were a prescription drug.

Finally, Part IV of this book is devoted to systems biology approaches to our understanding of circadian clocks. In general, our field has relied on models to enhance our conceptual understanding of the highly complex circadian system. The iterative approach of improving models with data from high throughput approaches and feeding back the results for experiments suggested therein—in essence, modern systems biology—is developing into a major tool in our chronobiology repertoire.

In the first chapter of this section, the principles of rhythm generation will be described from a mathematical perspective. It will become clear that feedback loops and coupling are fundamental concepts of oscillating systems. How these fundamentals are used to create rhythms that regulate, for example, transcription at many different times of day is highlighted in the second chapter of this part. The last chapters again help to appreciate the pervasiveness of circadian regulation by focusing on genome- and proteome-wide studies that uncovered circadian rhythms almost everywhere.

This volume adds up to an up-to-date review on the state of chronobiology, particularly with respect to molecular processes. It should be of special interest to chronobiologists, pharmacologists, and any scientists who is concerned with excellent protocols and methods.

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