Molecular Basis of Chronopharmaceutics

SHIGEHIRO OHDO,[1] SATORU KOYANAGI,[1] NAOYA MATSUNAGA,[1] AHMED HAMDAN[1,2]

[1]Department of Pharmaceutics, Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka 812-8582, Japan

[2]Department of Pharmaceutics, Faculty of Pharmacy and Drug Manufacturing, Pharos University in Alexandria, Alexandria, Egypt

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ABSTRACT: Many pathophysiological circumstances vary during 24 h periods. Many physiologic processes undergo biological rhythms, including the sleep–wake rhythm and metabolism. Disruptive effect in the 24 h variations can manifest as the emergence or exacerbation of pathological conditions. So, chronotherapeutics is gaining increasing interest in experimental biology, medicine, pharmacy, and drug delivery. This science and the plethora of information should be used intelligently for optimizing the effectiveness and safety of the drug, relying on the timing of drug intake. These chronopharmacological findings are affected by not only the pharmacodynamics but also pharmacokinetics of drugs. The mammalian circadian pacemaker is located in the suprachiasmatic nucleus. The molecular mechanisms are associated with *Clock* genes that control the circadian rhythms in physiology, pathology, and behavior. *Clock* controls several diseases such as metabolic syndrome, cancer, and so on. CLOCK mutation influences the expression of both rhythmic and nonrhythmic genes in wild-type tissues. These genotypic changes lead to phenotypic changes, affecting the drug pharmacokinetic and pharmacodynamic parameters. This review is intended to elaborate system regulating biological rhythms and the applicability in pharmaceutics from viewpoints of the intraindividual and interindividual variabilities of *Clock* genes. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association
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INTRODUCTION

The principal purpose of drug delivery is to formulate dosage forms meeting therapeutic demands relating to particular pathological cases. Circadian changes of physiological and pathophysiological functions throughout the daytime have brought a new approach to the evolvement of drug delivery. As a new and developing discipline, chronopharmaceutics has attracted considerable attention from academia and industry. Studies based on the individualization of pharmacotherapy, by monitoring drug concentrations in each patient, have been held to improve conventional pharmacotherapy to achieve the maximum effectiveness and/or safety.[1,2] The traditional classification has classified pharmaceutical variations into interindividual and intraindividual variabilities. The basic pharmacogenomic–pharmacogenetic studies only concentrate on the interindividual variability. Researchers have uncovered the molecular mechanism of the interindividual variation from numerous points of view and taking different levels, ranging from the genetic variation to the protein polymorphism depending on point mutations at the translation and posttranslation stages.[3–5] This hypothesis has hypothesized the emergence of diseases due to either upregulated or downregulated genetic expression of certain molecular targets. This concept did not take the intraindividual variability throughout the daytime in its attention. The clock and clock-controlled genes in mammals have been discovered since 1997.[6]

Both the intraindividual as well as the interindividual variabilities should be taken into our consideration, aiming at further improvement of rational pharmacotherapy. The circadian rhythmicity of biochemical, physiological, and behavioral processes may alter the potency and/or the toxicity of numerous medications depending on the administration time.[7–13] Chronopharmacotherapy has been described

Correspondence to: Shigehiro Ohdo (Telephone: +81-92-642-6610; Fax: +81-92-642-6614; E-mail: ohdo@phar.kyushu-u.ac.jp)

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by the medical society for curing many pathological states such as allergic rhinitis, nocturnal asthma, arthritis, congestive heart failure, myocardial infarction, stroke, and peptic ulcer disease. Chronopharmaceutics may be achieved by the dosing schedule of formulated tablets–capsules and the drug delivery system (DDS) in appropriate timing to keep matching between drug concentrations and rhythms in disease activity.[7,11] Pharmaceutical industries have extensively studied the underlying molecular mechanisms and have conducted clinical explorations, including myriad patients aiming at devising chronotherapeutic interventions with many pharmaceutical dosage forms and drugs. New technologies have been developed and tested for delivering active constituents precisely in a time-dependent fashion by bedside or ambulatory pumps to treat human diseases. Careful use of this new technology is the responsibility of chronopharmacologists to ensure that devices and clinical findings are well accepted by scientists currently involved in more classical research. However, drugs are still obeying the classical clinical practice and are administered regardless of the time of day. So, these chronopharmacological investigations should be summarized for clinical practice.

Homeostatic functions of steroid hormones and their receptors and many other physiological processes are subjected to the 24 h variation. Disquiet of these physiological rhythms is related to pathological state such as cancer, depression, and diabetes. *Clock* gene controls the etiology of several diseases such as metabolic syndrome, cancer, and so on. CLOCK mutation controls the genetic expression of both rhythmic and nonrhythmic genes in wild-type (WT) tissues. Chronopharmacotherapy is now depending on rhythm monitoring, rhythm manipulation, and overcome of rhythmic disruption focusing on the molecular clock system. This leads to more improvement and spreading of this science in the clinical practice. Chrono-DDS is the term used for the modern approaches of DDS that cope with the endogenous 24 h rhythm.[11,12] Contemporary technologies of pharmacotherapy have focused on pulsatile drug delivery, gene delivery, and antibody delivery, targeting specific molecular components for some diseases. *Clock* genes should be also important candidates for research and treatment. Therefore, this review is intended to elaborate an overview on the molecular mechanism regulating the biological rhythm based on *Clock* genes, the hieratical structure, the feasibility of this basic biology to be applied on the clinical practice, and the applicability in pharmacotherapy from viewpoints of the intraindividual and interindividual variability of *Clock* genes. Rodents such as mice or rats are mostly fed and active during dark period, namely nocturnal animals and their rhythmic pattern are totally different from that of diurnal human. The difference in act–rest cycle between nocturnal rodents and diurnal human should be considered in the interpretation of experimental findings described in this review.

BIOLOGICAL TIME STRUCTURE

The modern approach in the research of biological rhythms clearly reveals that biological processes are not constant over time. It is changeable in a highly organized, well controlled, and synchronized process. It includes the internal adaptation in response to external stimuli, namely zietgeber (from the German, "time givers") such as food and light. It is as diverse as cyanobacteria and humans. Biological time structure indicates the sum of non-randam and thus predictable time-dependent biological variations, including a spectrum of rhythm with different frequencies such as growth, development, and aging.[6,14–18] The endogenous period length (τ) of rhythms may be very short period, in the range of a second, such as in electrocardiographic and encephalographic tracings. Ultradian rhythms are an expression for rhythms of periods in the range of 30 min to 20 h, which are observed in many endocrine glands and sleep stages. Circadian rhythms with about 24 h period are entrained to the 24 h solar cycle and have been most explored now being applied into clinical practice as one of its numerous applications. Longer period lengths of rhythms of a week (circaseptan), a month (circatrigintan), and a year (circannual) are also known. The circatrigintan includes the menstrual cycle. Many rhythms seem to be genetically orthologous and thus endogenously generated in nature. Endogenous rhythms may or may not be controlled in their timing by environmental cues, synchronizers. Chronobiology objectively quantifies and investigates molecular mechanisms of biological time structure, including rhythmic manifestations of life.

CIRCADIAN TIME STRUCTURE

The circadian clock in mammals is expressed within pacemaker neurons of suprachiasmatic nucleus (SCN) that in turn maintain proper phase alignment of peripheral tissue clocks ubiquitously present in nearly all cells. Thus, the brain SCN clock provides "standard time" for all peripheral tissue clocks (Fig. 1).[11,12] The circadian clock consists of three components[6,14–18]: an input pathway adjusting the time by zeitgebers, a central oscillator generating the circadian signal in response to the input pathway, and an output pathway manifesting itself in the final circadian rhythmicity in physiology and behavior. The 24 h variation in light intensities is considered to be the major environmental input involved in circadian entrainment. Light signals stimulate photoreceptor cells in the retina, namely rhodopsin cone