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Chronobiology, drug delivery, and chronotherapeutics ☆

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Abstract

Biological processes and functions are organized in space, as a physical anatomy, and time, as a biological time structure. The latter is expressed by short-, intermediate-, and long-period oscillations, *i.e.*, biological rhythms. The circadian (24-h) time structure has been most studied and shows great importance to the practice of medicine and pharmacotherapy of patients. The phase and amplitude of key physiological and biochemical circadian rhythms contribute to the known predictable-in-time patterns in the occurrence of serious and life-threatening medical events, like myocardial infraction and stroke, and the manifestation and severity of symptoms of chronic diseases, like allergic rhinitis, asthma, and arthritis. Moreover, body rhythms can significantly affect responses of patients to diagnostic tests and, most important to the theme of this special issue, medications. Rhythmicity in the pathophysiology of disease is one basis for chronotherapeutics — purposeful variation in time of the concentration of medicines in synchrony with biological rhythm determinants of disease activity — to optimize treatment outcomes. A second basis is the control of undesired effects of medications, especially when the therapeutic range is narrow and the potential for adverse effects high, which is the case for cancer drugs. A third basis is to meet the biological requirements for frequency-modulated drug delivery, which is the case for certain neuroendocrine peptide analogues. Great progress has been realized with hydrogels, and they offer many advantages and opportunities in the design of chronotherapeutic systems for drug delivery via the oral, buccal, nasal, subcutaneous, transdermal, rectal, and vaginal routes. Nonetheless, innovative delivery systems will be necessary to ensure optimal application of chronotherapeutic interventions. Next generation drug-delivery systems must be configurable so they (i) require minimal volitional adherence, (ii) respond to sensitive biomarkers of disease activity that often vary in time as periodic (circadian rhythmic) and non-periodic (random) patterns to release medication to targeted tissue(s) on a real time as needed basis, and (iii) are cost-effective.

Keywords: Chronobiology; Chronopharmacology; Chronotherapeutics; Drug-delivery systems; Hydrogels; Human beings; Circadian rhythms

Contents

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1. Introduction

A primary doctrine of biology, medicine, and pharmacology is homeostasis, *i.e.*, relative constancy of the inner biological environment. The concept of homeostasis is based primarily on research conducted by Claude Barnard in France late in the 19th century and Walter Cannon in the US early in the 20th century. At that time laboratory methods were rather primitive; technology had yet to be developed to continuously monitor biological parameters, *e.g.*, heart rate, blood pressure, body temperature, activity level, and chemical methods were bulky, requiring as much as a pint of blood to determine the concentration of certain constituents. Also, data analysis and harvesting were difficult and slow, *i.e.*, computer hardware and software to detect and quantify time series data for rhythms were non-existent. In addition, most biological research was done during the daytime at the convenience of the diurnally active investigators and their staff. Thus, the understanding of animal and human biology today is based largely upon the findings of daytime investigations conducted during the waking span of diurnally active human beings plus daytime investigations conducted on nocturnally active laboratory mice and rats at a time that corresponds to their usual period of sleep.

The results of such single time-of-day studies are representative only of one particular circadian phase, *i.e.*, biological time during the 24 h. Numerous around-the-clock, menstrual cycle, and year-long studies show that the findings of human and animal research can differ greatly according to when, with reference to biological time, research is done [1,2]. Nonetheless, the doctrine of homeostasis continues to be taught to all biology, medical, and pharmacy students and continues to be the foundation for most biological and medical research and applications. Thus, it is not at all surprising that highly accomplished workers in these and related fields assume, *a priori*, that the time during the day, month, and year when biological and medical research is done or when preclinical and clinical studies of candidate medications are trialed is of minor or no consequence. Moreover, it is not surprising that a major goal of drug-delivery systems is constancy in the concentration of medications as an assumed means of achieving constancy in therapeutic effect and drug safety.

Today, a vast amount of literature clearly documents that biological processes and functions are not constant, but highly variable in a predictable-in-time manner as expressed by prominent rhythms of various period. It is further recognized that *both* homeostasis — constancy of the *milieu intérieur* — and rhythmicity — predictable-in-time variability of the *milieu intérieur* — are compatible concepts. Endogenous biological rhythms give rise to 24-h, menstrual, and annual oscillations in the set points at which homeostatic feedback systems are triggered.

Chronobiology is the study of biological rhythms and the mechanisms of biological timekeeping. Chronobiology is clearly