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Introductory Chapter: Circadian Rhythms and Their Molecular Mechanisms

Mohamed A. El-Esawi

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1. Introduction

A circadian rhythm is a biological process which shows an endogenous and entrainable oscillation of about 24 h. These 24-h rhythms are regulated by a circadian clock and are widely displayed in different organisms, including plants, fungi, animals, and cyanobacteria [1]. The endogenous circadian rhythms are adjusted to the environment by different surrounding cues, such as temperature, light, and redox cycles. In 2017, Jeffrey C. Hall and his colleagues have awarded the Nobel Prize in Physiology or Medicine for their discoveries of molecular mechanisms controlling the circadian rhythm. Circadian system runs as a result of four main components: (i) photosensitive retinal neurons and retinohypothalamic tract through which light signals come from the environment, (ii) internal circadian oscillator, generating rhythms and synchronizing them with the environment, (iii) signal paths transmitting information from the central regulator to peripheral rhythm generators, and (iv) peripheral rhythm generators (clock genes and proteins in peripheral cells).

In 1729, the French scientist Jean-Jacques d'Ortous de Mairan reported the first observation of an endogenous circadian oscillation and found that 24-h patterns in the movement of the leaves of the plant species *Mimosa pudica* continued even when the plants were kept in constant darkness [2, 3]. In 1896, Patrick and Gilbert reported that during a prolonged sleep deprivation period, sleepiness can increase and decrease within a period of approximately 24 h [4]. Furthermore, in 1918, J.S. Szymanski reported that the animals have shown their capability of maintaining 24-h activity patterns even in the absence or changes of external factors such as light and temperature. Circadian rhythms were also reported in the bees rhythmic feeding times in the early twentieth century. In 1935, circadian rhythms were also noticed in the fruit fly *Drosophila melanogaster* [5, 6]. In 1954, Colin Pittendrigh reported that temperature played a crucial role in eclosion rhythm, and the eclosion period was delayed without stopping when the temperature decreased, indicating that circadian rhythm is controlled by an internal

biological clock [6, 7]. The first clock mutant was identified in *Drosophila* and was called “period” (*per*) gene, which is the first discovered genetic determinant of behavioral rhythmicity [8]. Konopka, Jeffrey Hall, Michael Rosbash, and their team reported that *per* locus represents the center of the circadian rhythm and that loss of *per* locus stops circadian activity [9, 10]. Michael W. Young’s team also demonstrated similar roles of *per*, which covers 7.1-kilobase (kb) interval on the X chromosome and encodes a 4.5-kb poly(A) + RNA [11, 12]. The key genes and neurons in *Drosophila* circadian system were also discovered, for which Jeffrey C. Hall and his colleagues received the Nobel Prize in Physiology or Medicine 2017. Moreover, Joseph Takahashi identified the first mammalian circadian clock mutation (*clock*) in mice in 1994 [13]. However, recent reports revealed that the deletion of *clock* does not result in a behavioral phenotype, which questions its potential role in rhythm generation [14, 15].

2. Importance and molecular mechanisms of circadian rhythms

Circadian rhythms enable organisms to better prepare and capitalize on environmental factors (e.g., light and food) as compared to those that are not able to predict such availability. They are also important in regulating and coordinating internal physiological processes [16]. Photoperiodism, the physiological reaction of organisms to the length of day or night, is essential to both plants and animals, and the circadian system plays a crucial role in the measurement of day length. The rhythm is linked to the light-dark cycle. Plant circadian rhythms tell the plant what season it is and when to flower to better attract pollinators. A better understanding of plant circadian rhythms has applications in agriculture, such as helping farmers to extend crop availability and secure it against massive losses due to weather. In addition, *Bmal1* and *clock* proteins are accumulated during daytime forming the *bmal1/clock* complex which helps in activating the transcription of the *per* (*per1*, *per2*, and *per3*) and *cry* genes (*cry1* and *cry2*). The *per* and *cry* proteins also form a *per/cry* dimer which moves to the cell nucleus and inhibits the activity of the *bmal1/clock* complex, then leads to a reduction in *per* and *cry* protein expression. During nighttime, *per/cry* complex is destroyed, and the 24-h cycle begins. Another clock gene involved in the regulation of this cycle is *rev-erb-alpha*. The *bmal1/clock* complex activates the transcription of such a gene, which leads to the accumulation of *rev-erb-alpha* protein which in turn inhibits the transcription of the *bmal1* gene. In conclusion, this work would discuss the circadian rhythm phenomena and their molecular mechanisms in different organisms.

Author details

Mohamed A. El-Esawi

Address all correspondence to: mohamed.elesawi@science.tanta.edu.eg

1 Botany Department, Faculty of Science, Tanta University, Tanta, Egypt

2 The Sainsbury Laboratory, University of Cambridge, Cambridge, United Kingdom

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