Chapter 2

Circadian Rhythm and Chronobiology

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Abstract

All photosensitive organisms have a biological clock to cope with daily and seasonal circle of the earth. Biological clocks create circadian rhythms and regulate their processing according to cycle of the world. Circadian rhythm is an autoregulatory system and commands almost every physiological, biological, and biochemical functions of the mammalians. Therefore, biological clocks operate rhythmically with a period for a day, and this phenomenon is called as circadian rhythm. The process ongoing approximately 24 h rhythm in accordance with the meaning of the word (circa (approx.) dies (1 day). The essential purpose of biological clocks (in other word the organism's innate timing device) is the adaptation of the living organism to environment. Circadian rhythms refer to changes in the organism's approximately 1 day's physiological, biochemical and biological processes. In a molecular level, there are thousands of biological clocks in the human body. The main clocks in the human brain coordinate all these cellular clocks. Thus, the rhythmical phenomenon works in a harmony with the master clock and solar cycle. However, the natural factors within the body produce circadian rhythms the environment cues also affect them. The light is the main cue that affects biological rhythm. These light–dark cycles can control of the molecular structure of biological clocks. Changing the light–dark cycles leads to lengthen, shorten or completely absent of circadian rhythms. Dysfunction of circadian cycle leads to many health problems. The studies in chronobiology provide better understanding of the rhythmic metabolism and disrupted circadian rhythms. In recent years, numerous spectacular researches have been conducted in the field of chronobiology. These researches were intended to understand metabolic process of human body. However, the molecular and genetic mechanisms of circadian clocks still not clearly known. In this study, we aimed to investigate and summarize the recent progress about circadian biological research and understand how biological clocks govern the human metabolism.

Keywords: biological clocks, circadian rhythms, chronobiology

1. Circadian rhythms

Circadian rhythms are well-defined biological rhythmic activities ongoing 24-h time in human metabolism. Biological cyclical variation (circadian-biological-rhythm) is a physiological and kinetic event. It is clearly known that there is a molecular and neuronal connection between circadian clock and human metabolism. Thus circadian rhythms operate almost every functions of the metabolism from sleep/wake to fasting/feeding behavior through control of the cellular and organic system [1–3]. Biological rhythm is not exclusive to human being. Almost every living organism from plant and microorganism, to animal (in other words from single cell to multicellular) has own circadian rhythm [3]. Biological rhythms provide adaptation for living organism to environment both inside and outside. Circadian rhythms are the essential component of homeostasis in human body. Biological clocks are responsible to control physiological, homeostatic, behavioral and endocrine balance in organism [4]. In a nutshell, the repetitive fluctuations in biological, physiological and biochemical functions of the organisms within the period of 24 h are called circadian rhythms. Biological clock is a physiological system, which has the capacity to measure the passage of time in the living organism. Weger et al. have been shown that how the circadian clock contributes to adult stem cell function especially in the brain and neurogenesis [5]. The main issue is to provide the organism adaptation for daily and seasonal changes [6]. Biological rhythms are responsible for secretion of the hormones, the electrical activity of the hearth, body temperature, respiratory motion, and sleep-wakefulness. The main determinative circadian rhythm of the mammalian is sleep and wakefulness cycle [7]. Circadian rhythms, which take those 24 h, are examined in two parts: as nocturnal and diurnal rhythm. Nocturnal rhythm describes changes in the biological rhythm of the night, and diurnal rhythms refer to the biological rhythms that occur during the day. Human being has a diurnal activity pattern [8]. The other classification of the circadian rhythms is the infradian and ultradian rhythms. Infradian rhythms are the long rhythms that last more than from 24 h to weeks, months (examples are lunar −29.5 days- and semi lunar −14 days- rhythm. Ultradian rhythms are the short rhythms than 24 h (examples are tidal rhythms −12 h-). Ultradian rhythms are the important part of the circadian rhythms which regulate physiological functions of the body. When circadian rhythm regulated by natural environmental conditions, it is called entrained rhythm. In the case of the regulation isolated from environment, it is named as free-running rhythm or inner rhythm. There are well-defined patterns of physiological indices such as brain wave activity, cardiovascular, respiratory function, body temperature, and circadian rhythmicity [7]. The relatively new science "chronobiology" examines this biological cyclic phenomenon in living organisms. Chronobiology investigates the underlying mechanisms of chronomes which structures timing in organisms [8, 9]. Medical chronobiology is concerned with the chronopathology and chronopharmacology. Chronophysiology, chronopathology, and chronopharmacology are defined and still developing other fields about circadian rhythm. Chronophysiology examines how fitting in time setup the transaction of organisms and biological systems. Because of circadian rhythm underlie homeostasis of the body in case of dysrhythmia, the function of individual cells and so whole organisms affects negatively [10]. It has been shown that many diseases are related to dysfunction of the circadian rhythm. Consequently, chronopathology is concerned with the effect of biological rhythm in diseases formation. It deals with the pathology of diseases caused by disrupted rhythm. Chronopharmacology search for the timing of administration of medications and effects of pharmacological agents to biological rhythm [9, 11]. It has been proved that circadian dysrhythmia has significant impact on occurring and prognosis of the many health problems [12]. For this reason, comprehending that how biological clock works could provide amelioration for obesity, metabolic diseases, mental disorders, cardiac disorders, sleep disorders, and other health problems.

1.1. How does it work

Biological clock is a self-regulating clockwork mechanism that synchronizes oxidative and reductive cycles according to the solar cycle [13]. It provides controls of whole organism from the cell to the organ system. The main goal of circadian clock is to maintain the oscillations in a molecular level which enables light-sensitive organisms to coordinate nutrient storage and use it in accordance with the daily period of activity and rest [14]. Scientists' key goal is to understand how such circadian oscillations could be possible. In recent years scientists has been focused on set light to molecular mechanism of circadian clocks in humans [1, 3, 4, 8, 15]. It is well known that biological clocks are composed of specific proteins (molecules) throughout the body. Almost every cell contains an autonomous molecular clock. In mammals, the main circadian clock is located within the suprachiasmatic nuclei of the hypothalamus. The master clocks (suprachiasmatic nuclei (SCN) in the human brain coordinates all these cellular clocks [16]. Approximately 100,000 neurons have been identified that cluster in the suprachiasmatic nuclei of the hypothalamus extending from bilateral nuclei just above the optic chiasma. This location provides the SCN to receive the light for keeping the cycle in time [2, 7, 17–19]. The light directly from the retina adjusts biological clock and synchronizes within a daily cycle. There are special photoreceptive ganglion cells in retina, which contain light-sensitive pigment (it is called melanopsin). The melanopsin cells are stimulated by natural daylight especially short wavelength (blue light) [18]. Exposure to natural daylight stimulates nerve pathway in SCN. Moraes et al. reported that melanopsin cells play a role in synchronizing the central circadian clock with the day. They reported that melanopsin cells convey information about ambient light to the hypothalamic suprachiasmatic nucleus [18]. Blind people also have photoreceptive cells in their eyes. Because of that, they can usually respond to daylight. The light–dark signals are transmitted through the optic nerve to the suprachiasmatic nucleus, which uses them to reset the circadian clock each day [18]. Biological clocks not only need daylight to maintain its process, but also genes that influence the circadian rhythms. Biological clocks need both light and genes to keep it on track [19]. The brain needs lights to reset itself each day and to stay on the 24-h cycle. When humans kept in continuous darkness, the body's daily cycle tends to lengthen to about 25 h. Also people who lack genes which control the clock's cycle have could be lengthened cycles or absent completely. Main clock allows all the tissues in the body to synchronize with each other [17–19]. It has been reported that this mechanism is implemented by feedback loops of transcription and translation of core clock proteins [17]. This is an autoregulatory transcriptional feedback mechanism. It is known that most of genomes have transcriptional regulators, which transcribed in a rhythmic manner [19]. It has been shown that circadian clocks play a key role in mitochondrial oxidative metabolism [13]. It is well known that cellular redox (oxidation and reduction) status influences the activity of clock transcription factors [13]. Peek et al. identified the clock transcription feedback loop that produces cycles of nicotinamide adenine dinucleotide (NAD+). It is known that NAD+ is an important cofactor in oxidative metabolism. NAD+-dependent deacetylase activity affects protein acetylation in mitochondria. Peek et al. have been reported that circadian control of NAD+ bioavailability modulates mitochondrial oxidative function and organismal metabolism across the 24-h fasting and feeding cycle [13]. Thus, the molecular clock makes up the fluctuations, synchronized with the environment. Essentially circadian rhythms are endogenously generated process. But they could be modulated by external stimuli. Namely it could be affected by external stimuli such as temperature (heat-cold), light (light–dark), sound, food supply, time changing travel (jet lag) and social factors (in other words social jet lag). Circadian system regulates energy metabolism of the human body. Therefore, it governs the glucose, insulin, appetite and lipid metabolism. It has been shown that cellular metabolome—the complete set of small-molecule chemicals found within a biological sample—changes according to time of the day [17]. Dopamine and melatonin are prominent hormones of the circadian biology [20]. Melatonin is the main responsible hormone for human body's daily cycle. Melatonin receptors found a very wide distribution in the body. Suprachiasmatic nuclei control the secretion of melatonin. The primary physiological function of melatonin is to adjust light/darkness cycle in human body. Dark enables the endogenous secretion of melatonin which is constituted by the suprachiasmatic nuclei and entrained to the light/dark cycle. Light suppresses the secretion of melatonin [21]. The daily secretion of melatonin is a biochemical signal of night for preparing the organization to circadian rhythms. Melatonin secretion begins between 9 and 11 pm and peaks between 1 and 3 am. The other physiological functions of the h depend on melatonin signal. Melatonin affects cell surface receptors in central nervous system thus regulates sleep/wake cycle. Suprachiasmatic nuclei also drive the release of cortisol and growth hormone [7]. The biological rhythm of the human body could be summarized as: 00:00 Midnight, 02:00 Deepest Sleep, 04:30 Lowest Body Temperature, 06:45 Sharpest Rise in Blood Pressure, 07:30 Melatonin Secretion Stops, 08:30 Bowel Movement Likely, 09:00 Highest testosterone Secretion, 10:00 High Alertness, 12:00 Noon, 14:00 Best Coordination, 15:30 Fastest reaction time, 17:00 Greatest cardiovascular efficiency and Muscle Strength, 18:30 Highest Blood Pressure, 19:00 Highest Body Temperature, 21:00 Melatonin Secretion Starts, 22:30 Bowel Movements Suppressed [8, 10, 21]. Human physiological processes (including cerebral, renal, cardiac, hormonal and metabolic) are performed according to this cycle. As clearly seen in this cycle the human being could be arranged for feeding, sleeping, and activation time properly to their biological clocks.

1.2. Genes of circadian biology

Several genes have been identified in operation of biological clocks. In recent years, researchers have been focused on describing and analyzing clock gene expression [2, 15, 19]. It has been reported that one-third of all gene activity is regulated by the biological clock [2]. The circadian light receptors are encoded by the essential elements called cryptochromes (cryptochromic genes, CRY1 and CRY2). It has been accepted by the researches that cryptochromes play a fundamental role and they are the most important part of the circadian rhythm. In recent years, scientists defined myraid genes that govern circadian clocks such as BMAL1, CLOCK, CRY, PER, and TIM (specifically identified for the sleep process). It has been shown that these genes were found within the cells of nearly all body tissues but particularly active within the suprachiasmatic nuclei [22, 23]. The clock proteins which encoded by these genes in the human body could control the activity of these genes. Clock gene is the first identified gene (Vitaterna et al. 1994; Antoch et al. 1997). King et al. have identified BMAL1 gene (1997). BMAL1 gene is accepted as the heterodimeric partner of CLOCK gene. So CLOCK-BMAL1 accepted as transcriptional activator complex (Gekakis et al. 1998). Takahashi defined Period and Cryptochrome genes (Takahashi 2000). In 2002, it was defined "core circadian clock genes" (BMAL1, CLOCK, CRY1, CRY2, PER1, PER2) (Preitner et al. 2002). In the periodicity of the circadian rhythm, it has been found to be important of the regulation of the stability of the PER and CRY proteins by specific E3 ubiquitin ligase complexes [15, 22–25]. All these models describe the circadian clock in mammals. Increased recognition of the responsible genes in the circadian rhythm also provides an understandable processing mechanism of the human body. It has been known that the human body possesses internal time regulators which are genetically determined. Consequently, it is well known that a genetically manifested clock in the human body governs fundamental rhythmicity and enables homeostasis of the organism. It is clearly understood that the circadian rhythmicity is responsible for physiological, biological, and biochemical integrity of the human body. However, it is still unclear that how does circadian rhythmicity integrate with the physiologic systems. Although the numerous genes have been defined in process of the biological rhythmicity, the genetic and molecular mechanisms of circadian clocks also remain unclear. Learning more about the responsible genes for circadian rhythmicity will also help us to comprehend biological patterns of the human body.

1.3. Disrupted biological clocks

In mammals, the biological clock impulse energetic cycles to maintain physiologic stability. Biological rhythms are responsible for secretion of the hormones, the electrical activity of the hearth, immunity, hearth rate, blood pressure, coagulation, body temperature, hemodynamic, respiratory motion, and sleep-wakefulness [4, 12, 17, 19]. Therefore, circadian rhythmicity enables physical and mental goodness of the human body, irregular rhythms lead to various acute (delirium, hallucination) or chronic health problems (obesity, depression) [7, 27, 28]. It has been proved that many physiological variables are related to circadian rhythm. Each cell produces building blocks of amino acids. When desirable concentration is reached, the production stops. Clock genes govern these processes. In recent years, there is growing evidence about microbiome regulates that circadian clock genes [26]. It has been identified that the murine microbiome has circadian behavior and linked it to host feeding time. Liang et al. reported that the host circadian system influences the rhythmicity of the total load and taxonomic abundances in the fecal microbiota. They have reported that disruption of the host circadian clock by deletion of BMAL1 altered the fecal microbial composition [26]. It is well known that chronic sleep restriction alone could disrupt circadian transcription [29]. Circadian dysrhythmia directly causes diseases by cellular and visceral dysfunction in the human body. Cryptochromes play a key role in the diseases caused by disrupted biological clocks. It is well known that the mutation of the cryptochrome gene completely disrupts the circadian clock. Circadian dysrhythmia causes various abnormalities via impaired major metabolic proteins which play a key role in biological clocks [30]. It has been shown that circadian rhythms were severely disrupted in hospitalized patients. Disrupted circadian rhythm affects whole system in the body from sleeping/waking to digestive systems. Studies show that disrupted circadian rhythm contributes to several diseases [27–29]. Mostly circadian dysrhythmia and metabolic disorders such as obesity and metabolic syndrome are seen together [27, 29]. It has been reported that disrupted biological clocks lead to intolerance of glucose, insulin, and lipid metabolism [27–29]. Because of the glucose homeostasis is dependent on daily light–dark cycle, in case of the desynchrony glucose regulation impaired and this situation leads to metabolic syndrome even diabetes mellitus [12, 23, 29]. In addition, it has been reported in many studies that depressive and affective disorders were accompanied by disrupted sleep–wake patterns [10, 31]. In case of circadian dysrhythmia, the normal morphology of biological rhythms are changes in one or more of the aspects of the normal cycle. This could be a change in degree of fluctuation (mostly decreased amplitude), a phase shift (mostly phase delay), or disintegration of the cycle in a chaotic pattern. It has been shown that the severity of illness was correlated with degree of circadian disruption [7]. Scientist gradually understands that variety of the diseases are rhythmic disorders [10, 28–31]. The sleep disturbance is the first and overt symptoms of circadian dysrhythmia. The core temperature is one of the stable rhythms. It decreases consistently around 5 am. However, in chronic diseases fluctuates. It has been shown a correlation between severity of illness and degree of circadian disruption [7]. Cardiovascular system is a good example of organizing according to the oscillation of biological clocks. Most cardiovascular functions change with the circadian cycle. The longer-term effects of disrupted circadian rhythms are increased risk of obesity, metabolic problems, depression, mental disorders, cardiac and neurological events and even cancer. In recent years, there is a growing awareness about the negative effects of the technology to biological rhythm. Chronic exposure to artificial light causes numerous health problems from simply sleep disorders to many cancers [32]. It is known that sleep–wake disruption common in industrialized society depends on lifestyle. The main issue is how human being could keep their biological clocks in a regular system. As understood clearly in the biological cycle of human body, the daytime is optimum for food intake because of the biological rhythms peaks in the morning and afternoon [12]. Froy et al. showed that well-being could be achieved by resetting the circadian clock. They reported that timed feeding also arranges circadian rhythms [30]. In a similar way, it is obvious clearly the sleep and activation time. It is well known that there is a strong correlation between disrupted circadian rhythms and many health problems person. Based on this knowledge, scientists (consider the contrary) begun to search whether healing be guided by circadian rhythms as well. It has been shown that chronobiological interventions improved the clinical outcomes through amelioration of delirium and sleep disturbance [7, 30]. Understanding what makes biological clocks tick may provide treatments for many health problems from sleep disorders, obesity, mental health disorders, to jet lag. It can also improve ways for individuals to adjust to nighttime shift work. Learning more about the genes, which is responsible for circadian rhythms, will also help us understand biological systems and the human body.

2. Summary points

- Human being has a diurnal activity pattern.
- In a molecular level, there are thousands of biological clocks in the human body.

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- The main clocks in the human brain coordinate all these cellular clocks.
- Biological clocks provide adaptation for living organism to environment both inside and outside.
- Circadian rhythms are the essential component of homeostasis in human body.
- Biological clocks are responsible for controlling physiological, homeostatic, behavioral and endocrine balance in organism.
- Circadian rhythm is an autoregulatory system and drives almost every physiological, biological, and biochemical functions of the mammalians.
- The main purpose of circadian rhythm is to provide the organism adaptation for daily and seasonal changes.
- Chronobiology investigates the underlying mechanisms of chronomes.
- Cryptochromes play a key role in the diseases caused by disrupted biological clocks.
- A genetically manifested clock in the human body governs fundamental rhythmicity and enables homeostasis of the organism.
- There is a molecular and neuronal connection between circadian clock and human metabolism.
- Essentially circadian rhythms are endogenously generated process. But they could be modulated by external stimuli.
- Chronic exposure to artificial light causes numerous health problems from simply sleep disorders to many of cancer.
- The daytime is optimum for food intake because of the biological rhythms peaks in the morning and afternoon.
- Disrupted circadian rhythm affects whole system in the body from sleeping/waking to digestive systems.
- Understanding what makes biological clocks tick may provide treatments for many health problems from sleep disorders, obesity, mental health disorders, to jet lag.

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