Role of biological rhythms in the performance of physical activity

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Abstract Most organisms display various periodicities. Periodicity has been observed in humans in association with sleep, body temperature and hormone secretion. The molecular mechanisms involved are being elucidated by the investigation of clock genes in mammals. The relationship between biological rhythms and disease is also being studied. For example, myocardial infarction occurs more frequently in the morning, and disruption of biological rhythm is associated with obesity and diabetes. Some drugs have different medicinal effects depending on the time of dosing. Drug therapy known as chronotherapy, that takes into account the diurnal rhythm found in a given target disease, is being administered in some cases. Moreover, physiological responses and metabolism differ with time. Therefore, understanding the mechanisms underlying biological rhythms could enable the safe and effective performance of physical activity, in addition to potential medical applications. This review article outlines current understandings of biological rhythmicity and explores the relationship between biological rhythms and exercise, training, and sports.

Keywords : circadian rhythm, clock genes, chronoexercise, metabolism

Introduction

Many natural phenomena in living organisms display a periodicity that can be considered in terms of units such as year, month, and day. Of these, the intrinsic period of approximately 24 hours generated by the biological clock unique to each species is called the circadian rhythm. As will be described in detail, the circadian rhythm is synchronized by the light signal input from the eye. Remarkably, even visually impaired individuals who do not perceive light at all are known to synchronize circadian rhythms with day and night changes. Therefore, it is thought that there are factors other than light that can synchronize these rhythms, and physical activity is considered a candidate factor¹⁾. For example, based on the rodent wheel test used to analyze the rhythm of locomotor activity, running time-dependently regulates the phase of the circadian rhythm²⁾. In addition, exercising during the night causes the rhythm phase of melatonin secretion to be retarded in humans the next day¹⁾.

While it is certain that exercise affects the circadian rhythm as a synchronization factor, the detailed mechanism involved is unknown. Exercise could potentially be used as a way to improve rhythm disorders. When

abnormalities occur in biological rhythms, the internal environment, which includes the endocrine system and metabolism, is altered. Therefore, physical activity at an appropriate time could safely and effectively correct alterations in biological rhythms. In this review, we outline the fundamentals of various biological rhythms, molecular mechanisms of the circadian rhythm, and the circadian rhythms of physiological functions and their abnormalities. We also describe the relationship between physical activity and biological rhythms.

Biological rhythms

The biological clock is a mechanism that provides cycle fluctuations to living organisms, from a short cycle to a long cycle. The biological clock oscillates autonomously at a cycle similar to the length of the environmental cycle, and acts on various physiological functions to drive biological rhythms. Biological rhythms are classified into several categories according to cycle length. These include ultradian rhythms (less than 20 hours), circadian rhythms (20 to 28 hours), and infradian rhythms (28 hours or more).

Circadian rhythm. The most studied biological rhythms are circadian rhythms. The word “circadian” is derived from the Latin words *circa-* and *dies*, meaning “approximate”.

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mately” and “day,” respectively. In simple terms, the circadian rhythm represents a biological cycle that oscillates over the course of about one day. The word “circadian” was proposed by Halberg and is based on a statistically defined period of 24 ± 4 hours³⁾. A circadian rhythm is intrinsically formed and is determined by external stimuli such as light. The existence of a circadian rhythm must be confirmed in a constant environment without an environmental cycle. However, it is difficult to completely satisfy such conditions. Therefore, we regard the laboratory, with constant brightness and temperature, as a constant environment.

Circadian rhythms exist in most organisms such as animals, plants, fungi, and algae. The organism with the simplest circadian rhythm is the eubacterium cyanobacterium. Although most organisms have a circadian rhythm, the cycle under constant dark conditions differs depending on species and lineage. For example, the circadian rhythm of humans is 24.18 hours (i.e., 24 hours and 11 minutes)⁴⁾, while that of mice is shorter⁵⁾. Interestingly, there are differences in cycle length between mouse strains. For example, the circadian rhythm of Balb/cByJ mice is 22.94 hours, whereas that of C57/BL6J mice is 23.77 hours. Thus, circadian rhythms have unique values for each species and lineage.

Ultradian and infradian rhythms. In addition to circadian rhythms, other cycles exist as rhythms within living organisms. This section outlines rhythms other than circadian rhythms⁶⁾.

Ultradian rhythms are a biological rhythm with a shorter period than the circadian rhythm. A typical example of an ultradian rhythm is a sleep pattern. Although the sleep-wake cycle is 24 hours, it is not one continuous state. Several sleep cycles consisting of rapid eye movement (REM) sleep and non-REM sleep that last about 90 minutes each are recognized. REM sleep is characterized by rapid eye movements, depression of spinal reflexes, and an increase in heart rate and respiration.

Infradian rhythms have longer cycle rhythms than those

of circadian rhythms. These cycles may last for days, weeks, months, or even up to a year. The most characterized infradian rhythm is the circalunar rhythm. Circalunar rhythms are those synchronized to the phases of the moon and last 29.5 days. Many cycles are coordinated with the lunar month or with stages of the lunar cycle. For example, the average human menstrual cycle is approximately 28 days⁷⁾. Circatidal rhythms are another example of infradian rhythms, but these have little influence on mammals. There are various terms used to describe biological rhythms depending on the length of the cycle, and these are summarized in Table 1.

Oscillation mechanism of circadian rhythms

The type of rhythm that most influences the lives of mammals is the circadian rhythm. Studies of the circadian rhythm in rats and hamsters have demonstrated that the oscillation mechanism involves the central pacemaker present in the suprachiasmatic nucleus (SCN). Clock genes expressed in the SCN function as master regulators of biological clocks.

Circadian rhythm oscillator, the SCN. If animals are kept in a dark environment for an extended period of time, they will not synchronize to the 24-hour light-dark cycle, indicating the periodicity that the animals originally possess; this phenomenon is called free-running. These asynchronous periods are reset by stimuli such as light and dark. In mammals, the circadian clock center that produces a circadian rhythm is present in the SCN, within the hypothalamus. The term SCN was named because the left and right optic nerves are located directly above the intersecting part in the brain (Fig. 1). Approximately 20,000 neurons contained in the SCN of mice autonomously oscillate and create rhythms. Since there is an input from the optic nerve to the SCN, the phase of the biological clock can be modified by light. On the other hand, the output includes melatonin produced in the pineal gland, satiety center, feeding center, body temperature center,

Table 1. Various terms of biological rhythms

Terms of biological rhythm	Description of term
Circatidal rhythm	12.4 hours
Circadian rhythm	24 hours
Circabidian rhythm	2 days
Circaseptan rhythm	7 days
Circasyzygic rhythm	29.5 days
Circalunar rhythm	30 days
Circatrigintan	30 days
Circatrigintan	1 year
Ultradian rhythm	rhythm with shorter period than circadian rhythm
Infradian rhythm	rhythm with longer period than circadian rhythm

autonomic nervous system, and others.

Circadian rhythms can be investigated by evaluating the electrical activity of neurons in the SCN. The electrical activity rises during the day and falls at night. These rhythms continue even under constant dark conditions⁸⁻¹⁰. Furthermore, these daily rhythms are observed in nocturnal animals such as mice and diurnal animals such as humans¹¹.

History of clock gene discovery. It has been known for a long time that organisms have a circadian rhythm (Table 2). The first academic paper on the circadian rhythm was reported by de Mairan in France in 1729¹². The opening and closing movements of the flowers and leaves of plants according to periodic light and dark stimulation of day and night are called nyctinastic movements. De Mairan reported that nyctinastic movements continued even when placing a legume humble plant (*Mimosa pudica*) in the dark. However, the implications of this research were not recognized for about 200 years.

Konopka et al. first reported an animal with an abnormality in its biological clock¹³. *Drosophila* species were used as an animal model, and the researchers identified mutants with no circadian rhythm or cycles out of randomly generated mutations. The period gene (*Per*), was the first identified clock gene, and was reported almost simultaneously by several groups¹⁴⁻¹⁶. The first clock gene identified in mammals was the circadian locomotor output cycles kaput (clock) gene, *Clk*.¹⁷, which was identified by studying mutants with abnormal clock function from randomly generated mouse mutants. The mutants were first identified in 1994, and the causative gene was determined in 1997¹⁸⁻¹⁹. The first circadian rhythm-associated mutation in mammals was observed in a hamster; the *tau* strain was identified in 1988²⁰, and its causative gene was identified in 2000²¹.

Regulation of the circadian rhythm by clock genes. Circadian rhythms are regulated at the transcriptional level by several interacting clock genes²² (Fig. 2). The aryl

Fig. 1 The circadian clock center, SCN of mouse. The photograph is the brain of a formalin-fixed mouse, and the inserted picture (same as the area enclosed by the broken line) is the unfixed. Both pictures are the ventral plane of the mouse brain, and the left side of the pictures are rostral portion. You can see the suprachiasmatic nucleus where the two white optic nerves intersect (circles). Since the cells are dense in the SCN, they look reddish (arrows).

Table 2. The history of discovering the main clock genes

Year	Genes	Creatures	Researcher	Notes
1929		Humble plant	De Mairan ¹²⁾	The first academic paper describing the circadian rhythm
1971		<i>Drosophila</i>	Konopka et al. ¹³⁾	Discovery of <i>period</i> mutants
1973		<i>Neurospora crassa</i>	Feldman et al. ⁸⁸⁾	Isolation of <i>frequency</i> mutants
1984	<i>Per</i>	<i>Drosophila</i>	Reddy et al. ¹⁴⁾ Zehring et al. ¹⁵⁾ Bargiello et al. ¹⁶⁾	
1988		Hamster	Ralph et al. ⁸⁹⁾	Isolation of <i>tau</i> mutants
1994		Mouse	Pinto et al. ¹⁷⁾	Discovery of <i>clock</i> mutants
1997	<i>Clk</i>	Mouse	Antoch et al. ¹⁸⁾ King et al. ¹⁹⁾	
2000	<i>Csnkle</i>	Hamster	Lowley et al. ⁹⁰⁾	Identify the causative gene of <i>tau</i> as <i>casein kinase Iε</i> (<i>Csnkle</i>)

Fig. 2 Regulation of the circadian rhythm by clock genes. The ARNTL and CLK are core transcriptional proteins. ARNTL and CLK form heterodimers in the nucleus and regulate the expression of clock genes such as *Per* and *Cry* by binding to E-box sequences on DNA. The CLK/ARNTL heterocomplex specifically promotes transcription of *Per* and *Cry*, and translated products—the proteins PER and CRY—reciprocally suppress transcription mediated by the CLK/ARNTL heterocomplex. As a result, transcription of *Per* and *Cry* is weakened. Thus, there is a negative feedback loop in which the transcription product of the clock gene suppresses transcription of its own gene.

hydrocarbon receptor nuclear translocator-like protein 1 (ARNTL) and CLK are core transcriptional proteins. ARNTL is also called brain and muscle ARNTL-like 1 (BMAL1). ARNTL and CLK form heterodimers in the nucleus and regulate the expression of clock genes such as *Per* and cryptochrome (*Cry*) by binding to E-box sequences on DNA. The CLK/ARNTL heterocomplex specifically promotes transcription of *Per* and *Cry*, and translated products—the proteins PER and CRY—reciprocally suppress transcription mediated by the CLK/ARNTL heterocomplex. As a result, transcription of *Per* and *Cry* is weakened. Thus, there is a negative feedback loop in which the transcription product of the clock gene suppresses transcription of its own gene. This is the essence of the circadian clock, as this process takes approximately 24 hours to complete one cycle. In fact, the circadian rhythm disappears when the transcription and translation loop of these clock genes is defective²³⁾. In families with advanced sleep phase syndrome, a mutation has been found in a part of the *Per2* gene²⁴⁾.

Central clock and peripheral clock. Recent studies have revealed that clock genes exist not only in the SCN, but also in various peripheral tissues, such as the liver, kidney, and heart²⁵⁾. For this reason, the clock in the SCN is

called the central clock, and clocks in other tissues are called peripheral clocks. The circadian rhythm control center is the SCN of the hypothalamus, which has a role as a pacemaker that regulates the circadian rhythm of the whole body. The SCN was traditionally considered the only circadian rhythm oscillator, and the circadian rhythm fluctuations of various physiological phenomena observed in other peripheral tissues were considered to be dependent on the SCN. However, in recent years, it has become clear that each tissue and cell has a small intracellular clock mechanism independent of the SCN²⁶⁾.

There are also some reports on the interrelationship between the central clock and the peripheral clock. For example, one study investigated the rhythm of peripheral clock genes by performing a parabiosis surgery to connect the body fluid circulation of SCN-disrupted mice and normal mice²⁷⁾. When performing parabiosis surgery, rhythms recovered in the liver and kidney in SCN-destroyed mice supplied with body fluid from normal mice, but did not recover in the heart, spleen, and skeletal muscle. Thus, at least in the liver and kidney, it was found that substances derived from the SCN or regulated by the SCN are necessary for maintaining the circadian rhythm of the peripheral clock. The relationship between the central clock and the peripheral clock is not only mediated by the SCN. In

elderly mice, signaling between the central clock and the peripheral clock is weakened because sympathetic regulation decreases with advanced age. For this reason, it was reported that synchronization induced by light, exercise, or stress was suppressed, while synchronization induced by diet was enhanced²⁸⁾.

Currently, the relationship between the SCN and other peripheral tissues (peripheral clock) in circadian rhythm control is thought to be a relationship resembling that between a conductor and a player in an orchestra. In other words, although small clocks present in each tissue and cell can independently display a rhythm (player of each instrument), the SCN (conductor) synchronizes the rhythm of each component, so that one rhythm is made to oscillate. In this way, the SCN is the center of the mammalian circadian clock, but an autonomous circadian clock oscillator is also present in most tissues and cells. This indicates that the circadian clock not only controls rhythms such as those modulating sleep, but also controls physiological functions in individual cells.

Clock genes and physiological rhythms

Circadian rhythms are important in organisms including humans, and clear circadian rhythms exist in brain waves, hormone secretion, cell regeneration, and many other vital activities. In particular, there is a strong reciprocal relationship between circadian rhythm and metabolism. The circadian clock regulates many metabolic pathways, while metabolites and feeding behavior regulate the circadian clock²⁹⁾. This section outlines the relationship between clock genes and rhythms of physiological functions, especially metabolism.

Various rhythms of physiological functions. Today, in many countries, day and night shift work focusing on efficiency is on the rise, and a heavy burden is placed on maintaining the circadian rhythm. In Japan, it has been shown that shift work increases obesity and the risk of death from ischemic heart disease³⁰⁾. In this way, it is thought that an irregular life structure disrupts the circadian clock, and physiological functions such as metabolism become abnormal.

Most of the target genes of ARNTL1 are metabolism-related genes³¹⁾. Also, a metabolome analysis demonstrated that the amounts of many metabolites are modified in an ARNTL1-dependent manner³²⁾. As evidenced by these results, *Arntl1*-deficient (*Arntl1*^{-/-}) mice show abnormal lipid metabolism even when given a normal diet, while the abnormality is corrected by feeding a high fat diet³³⁾. The respiratory quotient of *Arntl1*^{-/-} mice shows higher values throughout the day than that of control mice, indicating that ARNTL1 is involved in the utilization of fat as an energy source. ARNTL1 is also involved in adipose differentiation, as *Arntl1*^{-/-} murine embryonic fibroblasts (MEFs) do not differentiate into adipocytes³⁷⁾. In addition,

ARNTL1 regulates blood glucose levels through control of insulin secretion in the pancreas. *Arntl1*^{-/-} mice show a marked rise in blood glucose level, which is attributed to a decrease in the blood insulin level^{33,34)}. Pancreatic-specific *Arntl1*-deficient mice have decreased insulin secretion and become diabetic²⁹⁾. In systemic *Arntl1*^{-/-} mice and in pancreas-specific *Arntl1*^{-/-} mice, both the number and size of pancreatic β cells are decreased.

CLK-ARNTL1 dimers appear to be involved in the regulation of many metabolic pathways, including lipid metabolism³⁵⁾. *Clk/Clk* mutant mice do not display a circadian rhythm, overeat, become obese, or exhibit metabolic syndrome³⁶⁾. In liver-specific *Arntl1*-deficient mice, circadian expression of genes important for glucose metabolism, such as glucose transporter 2, is absent. This results in the mice being hypoglycemic during the fasting phase (i.e., at a time of little or no glucose ingestion) of the feeding cycle²⁹⁾. Transgenic mice overexpressing mutant *Cry* displayed a marked increase in blood glucose³⁸⁾. In an insulin tolerance test, mutant *Cry*-overexpressing mice showed a similar degree of insulin sensitivity as control mice, but glucose tolerance was low, suggesting that CRY controls insulin secretion.

The coupling of the circadian clock and metabolism is recognized in various organisms, from humans to yeast. Many nuclear receptors also undergo circadian regulation by CLK-ARNTL heterodimers. For example, CLK and ARNTL1 regulate the expression of peroxisome proliferator-activated receptor α (PPAR α) by binding to an E-box element of the *Ppara* promoter, whereas PPAR α regulates the expression of *Arntl1* by binding to a PPAR α response element in the *Arntl1* promoter²⁹⁾. PPAR α is mainly expressed in the liver and brown adipose tissue where fatty acid β oxidation is active, and its agonist fibrates is clinically used for lowering lipids. Diurnal variations in glucose and lipid metabolism may occur according to such a mechanism. PER2 binds to various nuclear receptors, including PPAR γ and PPAR α , and regulates binding to their target promoters^{39,40)}. PPAR γ is mainly expressed in adipose tissue and macrophages, and its agonism, using a thiazolidine derivative, is clinically used to treat diabetes. Therefore, changes in fat metabolism are observed in *Per2*-deficient mice. Thus, disturbances in circadian rhythm regulation promote metabolic abnormalities.

Regulation of metabolism by the clock gene. The feeding behavior of mice follows the circadian clock, and mice mainly feed during the active phase of the dark period. However, if diet is restricted so as to eat at noon, circadian gene expression in the liver is reversed. In addition, mice loaded with a high fat diet during the day have a higher degree of obesity compared with mice loaded with the same high fat diet at night, indicating that the timing of ingestion is important for metabolism. In addition to timing, the quality of the diet is also important, as a high fat diet load changes the circadian rhythm of the

liver. Thus, metabolism can control the peripheral clock. The levels of metabolic products (glucose, amino acids, phospholipids, etc.) in plasma oscillate in a circadian manner. The circadian rhythm of metabolites, called the output of the circadian clock, is itself the input into the circadian clock.

Chronotype and clock genes. There are individual differences in the phases of biological rhythms in humans, and there are large individual differences in the daily fluctuations of sleep awakening patterns, vigor, and mood. This representative personality is called a chronotype—for example, a morningness or an eveningness. From epidemiological surveys and genetic studies to date, the chronotype is a phenotype of biological clock function characteristic of individuals. Duffy and colleagues reported that the period of rectal temperature was shorter for morningness^{41,42}. In addition, Brown and colleagues showed that the *Arntl1* mRNA expression cycle in dermal fibroblasts was short in morningness and long in eveningness⁴³. There are chronotype differences related to the phases of plasma cortisol⁴⁴, plasma melatonin⁴⁴⁻⁴⁸, and deep body temperature^{44,46-51}, which are representative indicators of circadian rhythm in humans. These phases have a delay of about two hours in eveningness compared with that of morningness. Thus, although there are differences in the rhythms of physiological functions depending on the chronotype, analysis at the clock gene level requires further investigation.

Exercise, training, sports, and circadian rhythm

Diurnal variation is observed in various biological functions of humans. Due to the rapid rise of cortisol at the time of waking, we regulate our body so that we can wake from sleep and function. The body gradually shifts to a state of sympathetic dominance from a state of parasympathetic dominance during sleep.

Endocrine function, especially the secretion of hormones caused by the hypothalamus, becomes active during the night while sleeping. “Sleeping child grows up” is an idiomatic phrase that expresses biological rhythms well, as the blood concentration of growth hormone (GH) peaks from 2 to 4 o’clock in the morning, a typical sleeping period. In the absence of sleep, the rhythm will collapse, and GH will not be normally secreted. On the other hand, the function of the cardiovascular system increases in response to the activation of sympathetic nerve activity at the time of waking, and peaks in blood pressure and heart rate occur in the evening. Cardiac arrhythmia attacks frequently occur shortly after waking or in the evening, and are due to diurnal variations in cardiovascular function. Thus, the circadian rhythm can be observed in various physiological functions. Circadian rhythms are also observed at the cellular level. For example, it has been shown that there is a diurnal variation in cell divi-

sion, but the peak of the division cycle differs depending on the type of organ and tissue.

Based on these findings, the potential importance of treating individuals in a time zone where treatment effect is high, according to changes in the biological rhythm mediated by the biological clock, has been recognized. Chronotherapeutics is based on the idea of chronopharmacology, in which medicinal efficacy differs according to treatment time and timing. For example, the activity of hydroxymethylglutaryl-CoA (HMG-CoA) reductase, the rate-limiting enzyme of cholesterol biosynthesis, shows a circadian rhythm, which peaks at night. Cholesterol-lowering drugs, such as statins, are most effective before going to bed. Similarly, by performing physical activity at the appropriate time, safe and efficient results may be achieved. Some researchers call this concept chronoexercise, which focuses on the influence of the temporal aspect of exercise on metabolic response. It will be necessary to study the association between exercise, training, and sports and circadian rhythm to fully characterize this complex relationship.

Temporal effectiveness of exercise, training, and sports.

The correlation between exercise, training, and sports performance and time of day has been examined extensively. The majority of these studies report that performance increases from morning to afternoon or evening. Technical skills in particular have been found to be greatest in the afternoon⁵²⁻⁵⁴. The peak is reached in the evening, such as muscular strength and anaerobic performance⁵⁵⁻⁶¹. Technical skills require a higher degree of exercise control, so they peak earlier⁶². Details have been described in other reviews⁶³. For example, a study of soccer skills revealed that juggling is better in the afternoon⁵⁴, while chipping is more accurate in the afternoon⁵⁴ or evening⁶⁴. The accuracy of short and long badminton serves was found to be higher in the afternoon than in the morning and evening, while consistency of the serves did not vary across the day⁵².

Diurnal variation may be influenced by several factors. One such factor is body temperature. By raising body temperature in a warm environment, diurnal variation can be reduced or eliminated⁶⁵⁻⁶⁷. Similarly, a warm environment improves diurnal variation in the morning⁶⁸. However, a rise in body temperature due to warming is not always effective in improving diurnal variation⁶⁹⁻⁷³. In a study in which warming was applied in the morning to increase body temperature to the same level as evening body temperature, did not produce any change in swimming performance⁷².

The circadian rhythm has an important property called temperature compensation, whereby the cycle length is kept constant over a certain temperature range. In order for the biological clock to accurately monitor intrinsic rhythm, it is necessary that it not be influenced by the external environment. Because the outside temperature

varies greatly depending on the season and location, it is critical to synchronize to the 24-hour period of the outside world, regardless of the temperature. Therefore, temperature compensation is an indispensable property for forming a stable circadian rhythm⁷⁴). The circadian clock cycle is approximately 24 hours in length, and is mostly unaffected by temperature. Therefore, it is considered that high ambient temperature will not strongly influence the expression of the clock gene. However, since there are many reports that high ambient temperature regulates exercise, training, and sports performance, high ambient temperature could be indirectly involved in modifying the biological clock by inducing a physiological change. In addition, it is also known that in the absence of light fluctuations, a given phase can be tuned with a sensitivity of $\pm 2^\circ\text{C}$ due to a higher temperature during the day and a lower temperature at night. Therefore, there is the possibility that a phase change due to the temperature change may be affected⁷⁵⁻⁷⁷).

The influence of exercise, training, and sports on circadian rhythm and hormone secretion. Blood hormone levels are closely related to physical activity. Kawahara et al. investigated the association between exercise and blood hormones under conditions of 70% and 90% maximal oxygen consumption ($\dot{V}\text{O}_2$ max) in young and aged individuals⁷⁸). Under the 90% $\dot{V}\text{O}_2$ max condition in young individuals, blood hormone levels increased, including noradrenalin, adrenalin, aldosterone, antidiuretic hormone, and glucagon. Some hormones (noradrenalin, adrenalin, aldosterone, antidiuretic hormone) were elevated in both young and aged individuals. On the other hand, blood GH levels were elevated and blood insulin levels were lowered only after exercise in aged individuals.

Exercise augments the nocturnal prolactin rise in exercise-trained men⁷⁹). In healthy subjects without external stressors, cortisol, dehydroepiandrosterone (DHEA) and testosterone are secreted in a circadian pattern⁸⁰⁻⁸⁴), with the highest concentrations observed in the morning and the lowest in the evening. Aerobic exercise significantly increased DHEA levels at two time points of the day only in male subjects⁸⁵). Thus, the effect of exercise on the circadian rhythm of hormone secretion may have a sex difference.

Wheel running is known to accelerate re-entrainment of behavior rhythm to a phase-advanced light/dark (LD) cycle in hamsters⁸⁶) and mice⁸⁷). The effects of wheel running on re-entrainment depend on the time of day, and mistimed wheel running interferes with re-entrainment of circadian *Per1* expression rhythms in the mouse skeletal muscle and lungs⁸⁸). There are few reports about clock gene expression. Since exercise and biological rhythms are closely associated, further research is needed in the future to elucidate potential mechanisms.

Summary

In this review, we outlined the major characteristics of the circadian rhythm. The circadian rhythm exerts control over the functionality of the body and is essential for homeostasis. Therefore, a rhythm abnormality may lead to an abnormality in physical function. Detailed molecular and physiological analyses have led to a greater understanding of the circadian rhythm. As a result, chronotherapy based on chronopharmacology has been undertaken.

A similar way of thinking can be applied to physical activity. Exercise, training, and sports can modify the circadian rhythm of various physiological parameters such as hormone secretion. Therefore, physical activity, while focusing on the rhythm of a particular physiological parameter, may achieve a maximum effect. However, early morning exercise, training and sports, where myocardial infarction is likely to occur, must be performed with caution. Thus, safe and effective exercise, training, and sports can also be implemented in consideration of the circadian rhythm. The concept of “chronoexercise” is still immature and represents a potential academic field of the future.

Conflict of Interests

The authors declare that there is no conflict of interest regarding this article.

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