REVIEW
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Circadian Rhythm, Hypothalamo-Pituitary Adrenal Axis, and Immunity: Physiological and Pathological Examples

Sirkadiyen Ritim, Hipotalamo-Hipofizer Adrenal Aks ve Bağışıklık: Fizyolojik ve Patolojik Örnekler

ABSTRACT
All living organisms, from single-celled microorganisms to humans, have to adapt to changing environmental conditions to maintain their survival processes. There are biological clocks in the body, which are related to the circadian rhythm and have a hierarchical organization. The master circadian clock is located in the suprachiasmatic nucleus (SCN) of hypothalamus. SCN maintain body rhythms in synchronous with the light-dark cycle in the external environment. There are also peripheral oscillators that work in coordination with SCN. Neurological, endocrinological, and immunological functions in the body are under the influence of circadian and seasonal rhythms. Melatonin and cortisol (corticosterone in animals) are among the most important hormones that show circadian rhythm in the body. The body adapts to daily and seasonal changes with biological rhythms regulated by biological clocks. It is well known that the immune system is affected by the external environment. Changes in endocrine system, hypothalamo-pituitary adrenal (HPA) axis, and immune system are marked, especially depending on the seasonal changes. Therefore, the immune system has close relationship with the circadian rhythm. Understanding relationship between physiological regulation of the circadian rhythm, HPA axis and immune activity is important for to keep our body in healthy conditions and struggle with the diseases as well. In current review, the interaction and relationship of genes and proteins related to the circadian rhythm with HPA axis and immune system parameters are discussed with both physiological and pathological examples.

Key Words:
Circadian rhythm, Immune system, Hypothalamo-pituitary adrenal axis, Health, Disease

ÖZ
Tek hücreli mikroorganizmalardan insanlara kadar, canlılar değişen çevre koşullarına uyum sağlamak zorundadır. Sirkadiyen ritim bu adaptasyonla ilişkili en önemli mekanizmadır. Vücutta sirkadiyen ritimle ilişkili, hiyerarşik organizasyona sahip, biyolojik saatler bulunmaktadır. Master sirkadiyen saat, hipotalamusun suprakiyazmatik nükleusunda (SCN) yer almaktadır. SCN, vücut ritimlerini dış ortamdaki aydınlık-karanlık döngüsüyle senkronize halde tutar. Merkezi saat olan SCN ile koordineli çalışan, periferal osilatörler de mevcuttur. Vücutta nörolojik, endokrinolojik ve immünolojik fonksiyonlar sirkadiyen ve mevsimsel ritimlerin etkisi altındadır. Vücutta sirkadiyen ritim gösteren hormonların başında melatonin ve kortizol (hayvanlarda kortikosteron) gelmektedir. Vücut, günlük ve mevsimsel değişikliklere biyolojik saatleri vasıtasıyla düzenlenen biyolojik ritimlerle uyum sağlamaktadır.

Bağışıklık sisteminin dış çevreden etkilendiği iyi bilinmektedir. Özellikle mevsimsel değişikliklere bağlı olarak endokrin sistemde, hipotalamo-hipofizer adrenal aksta ve immün sistemde değişiklikler kendini belli etmektedir. Bununla birlikte immün sistem sirkadiyen ritimle de sıkı ilişkiye sahiptir. Sirkadiyen ritmin fizyolojik regülasyonu ve immün aktivite arasındaki ilişkinin anlaşılması sağlıklı yaşam ve hastalıklarla mücadele bakımından önem arz etmektedir. Yazımızda sirkadiyen ritimle ilişkili gen ve proteinlerin immün sistem parametreleri ile etkileşimi ve ilişkisi güncel fizyolojik ve patolojik örneklerle ele alınmaktadır.

Anahtar Sözcükler:
Sirkadiyen ritim, İmmün sistem, Hipotalamo-hipofizer adrenal aks, Sağlık, Hastalık

INTRODUCTION

All living organisms, including humans have very close relationships with their environment. Since environmental conditions are dynamic factors, they constantly affect the body functions. Some events on the Earth occur cyclically such as day and night or they occur seasonally. Therefore, every organism must act in harmony with the environment in which they live. This is an indispensable condition for maintaining homeostasis and acquiring adaptation skills. There are specialized cell groups in the body that detect cyclical changes with the external environment and provide appropriate harmony. The most important regulator of this harmony is the suprachiasmatic nucleus (SCN), located in the hypothalamus. The SCN is to ensure the coordination of circadian rhythms in the body. This function of the SCN is supported by other circadian oscillators from the peripheral sections of the body. The circadian rhythm data is presented to the brain by the SCN. The brain, which is the control center of the body, communicates with all body cells with endocrine factors. This process is called neuroendocrine activity and it enables the body to act as a whole. Another factor with which the endocrine system interacts is the immune system. Thus, the integration of nervous stimuli with endocrine and immunological activity is ensured. This integration is known as the neuro-immunoendocrine system. Some hormones have special importance in the functionality of the neuro-immunoendocrine activity and its harmony with the circadian rhythm. Among the most important of these endocrine factors are melatonin produced from the pineal gland and glucocorticoids (cortisol in humans, corticosterone in animals) secreted from the adrenal gland. The hypothalamo-pituitary adrenal (HPA) axis must be activated in order to release cortisol from the adrenal gland. It is known that HPA axis activity has a circadian rhythm. However, the HPA axis might be activated by acute or chronic stress as well. Changes in HPA axis activity affect the immune system. In our review, important factors related to this interaction are discussed. Moreover, the effects of the circadian rhythm on the immune system physiology, as well as the pathophysiological conditions are discussed with current data.

CIRCADIAN RHYTHM

The concept of circadian rhythm was first defined by Franz Halberg using the Latin words “circa” (about) and “diem” (day) (1). Since then, this concept has been used to describe the cyclical, physiological, and behavioral effects of the light and dark cycle on the organism caused by the 24-hour rotation of the earth revolving around the sun on its axis. Such internal rhythms are valid in organisms from photosynthetic prokaryotes to mammals depending on the presence of endogenous circadian clocks, which regulate behavioral and physiological processes with their functions of adapting and coordinating the internal environment with external cues (2, 3). Thus, the organism can predict periodic changes to adapt to changing conditions and regulate its functions according to the time of day using circadian rhythms. The oscillators associated with the circadian rhythm consist of two main interrelated parts: the primary structure of these systems is the central clock located in the SCN of the hypothalamus and the others are peripheral clocks distributed throughout the body (4). The maintenance of circadian rhythms, formed by the alignment of internal circadian oscillators to external stimuli, relies on external cues such as light pattern, temperature, and food intake. The primary external synchronizer of circadian rhythms consists mainly of the daily light-dark cycle. In mammals, signals generated by light contact with the eyes are transmitted to the SCN via the retino-hypothalamic pathway. Thus, the SCN, a master oscillator, primarily uses the light-dark cycle to synchronize the body with the light signal (5). In order to maintain homeostasis, the circadian rhythms formed on the basis of the sleep-wake cycle must not be disturbed. In the coordination of the SCN, with the participation of peripheral oscillators, many physiological functions such as endocrine activity, immune activity, digestive system, body temperature, and blood pressure regulation, as well as psychophysiological functions such as sleep-wake, emotional state, learning-memory, feeding behavior are maintained in harmony (4, 6).

MOLECULAR PHYSIOLOGY OF THE CIRCADIAN RHYTHM

The mammalian circadian clock is a complex structure formed by a combination of feedback-feedforward mechanisms. In particular, transcription of BMAL1 (brain and muscle Arnt-like protein 1 (also called as ARNTL) and CLOCK (circadian locomotor output cycles kaput) genes, or its related gene NPAS2 (neuronal PAS domain-containing protein-2), leads to the heterodimerization in cytoplasm of the BMAL1 and CLOCK complex, which translocate into the nucleus where it binds to E-Boxes of clock-regulated genes (7). Clock genes and clock-related genes have a triple helix-loop-helix structure. The transcription factors are Clock, Bmal1, three Period genes Per1, Per2, and Per3, two Cryptochrome genes Cry1 and Cry2, three orphan nuclear receptors Nr1d1 (nuclear receptor family subclass group 1, member 1), Rev-Erb-α and Ror (retinoic acid-associated orphan nuclear receptors)-α. Transcription factors are thought to provide circadian regulation of gene expression (8) (Figure 1).

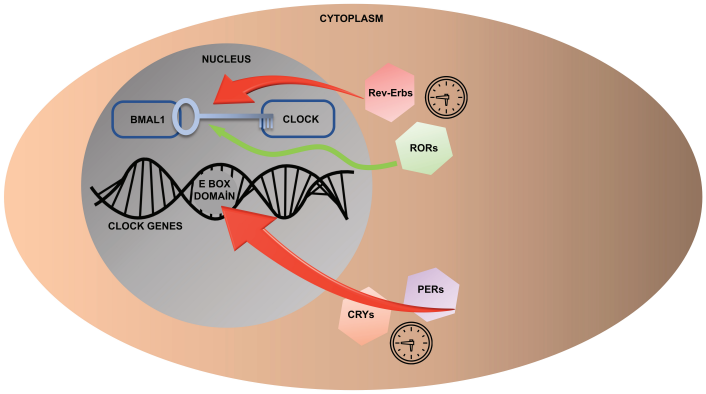

Figure 1. Schematic of BMAL1/CLOCK gene transcription and feedback mechanisms. (Modified from Ref. 8).

The transcriptional feedback pattern of circadian rhythm in mammals is mediated by the proteins Cry1, Cry2, and Per1, Per2. Clock and Bmal1 bind to the E-promoter region on the Per and Cry genes, inducing the expression of these genes. Per and Cry then heterodimerize and pass from the nucleus to the cytoplasm, inhibiting the gene expression induced by Clock/Bmal1 (9). Phosphorylation of related proteins occurs by casein kinases (CK1 ε and CK1δ) targeting Per proteins and adenosine monophosphate kinases (AMP kinase) targeting Cry proteins. In the following process, phosphorylated proteins are degraded by the ubiquitin ligase complex (10). With the breakdown of the Per/Cry complex, the cycle starts again. Besides the Per and Cry genes, BMAL1/CLOCK also activates the transcription of the Rev-Erb-α and Ror-α. This activation is inhibited by Rev-Erb-α, which binds to the retinoic acid-associated orphan nuclear receptor element of Bmal1, while it is activated by Ror-α (11). Other genes controlled by the circadian clock can also be regulated by the molecular clock since they contain an E-box in their promoter region (9). Regulation of clock genes with nuclear receptors such as Rev-Erb-α, Ror-α, and PPAR-α provides rhythmic realization of many hormones, nutritional signals (fatty acids and derivatives), and cellular redox status (12).

MASTER CLOCK SCN AND ITS LIGHT-MODIFIED CYTOKINE ACTIVITY

It is known that light is the most important zeitgeber. The melanopsin photopigments in the retina are activated by light stimuli, and this stimulation sets the internal clock's timer (13). The wheels begin to spin when the mainspring is wound, much like a mechanical clock. As a result, the clock spring is squeezed, activating the other component. While the interlocking gears continue to rotate exactly and the spring continues to discharge at the same rate, the spring starts to cycle down. When light stimuli reach the SCN in mammals, the primary wheel starts to turn. The central wheel attached to this circuitry is turned by the main circuit, which also causes the expression of the clock-related transcription factors BMAL1 and CLOCK. The clock-related Per and Cry genes' promoter region is located in this wheel. The second, minute, and hour circuits linked to the same vertical axis start spinning when the promoter is activated. Numerous clock-related genes are found throughout the body of mammals. One gear of the minute wheel is turned by one complete rotation of the second's wheel. A single gear on the clock wheel completes one full rotation of the minute hand gear. A 12-hour period is represented by one full rotation of the scorpion gear on the watch dial, while a 24-hour period is represented by two full revolutions (14, 15).

In mammals, SCN lesions cause sleep disturbance, and cause changes in melatonin production, primarily due to disruption of the circadian rhythm (16, 17). This situation affects many other body functions over time. The SCN network output has a sinusoidal pattern, but the relationship of this functioning to behavior varies depending on whether the organism has nocturnal or diurnal activity. In nocturnal animals such as rodents, the lowest level of SCN activity occurs in the active period, while in humans with diurnal rhythm, the peak in SCN activity occurs in the active period (18). A number of clock genes such as Per1 and Per2 in the SCN are light sensitive (19). It has been reported that dim light during the night affects the expression of per2 in the SCN of birds, leading to the loss of standard 24-hour cycles of Ror-α and Cry1 (20). In the same study, a decrease in interleukin (IL)-1β and Toll Like Receptor (TLR)-4 mRNA transcripts were also detected. In another study, it was determined that IL-1β and IL-10 levels were affected in birds exposed to dim light at night (21). The effect of clock gene changes on cytokine expression was also found to be valid in zebrafish (22). In the aforementioned study, it was determined that changes in Per1 and Per2 genes affect cytokine expression, and changes in per1b affect the neutrophil count. In a mammalian study of the photic effect of immunity, it was suggested that mice kept in constant-dark conditions showed a mortality rate three times higher than those in the normal light: dark cycle, but this was not associated with myeloid expression of BMAL-1 and CLOCK (23). Additionally, it was noted that when sepsis model mice with cecal ligation puncture were exposed to high-illumination blue light imitating early morning light, the rate of sepsis and organ damage decreased (24). The fact that other mammals have nocturnal rhythms like rodents and diurnal rhythms like humans is one of the most significant contrasts between them. The anti-phase expression of BMAL1 and Per2 in humans and mice is the most common illustration of this circumstance (25).

CIRCADIAN RHYTHM AND IMMUNE SYSTEM

It is known that the immune system, including innate and adaptive immunity, shows circadian variations (7). The first data on the relationship of the immune system with the circadian rhythm in humans date back to 75 years ago (26). In that study, it was reported that the amount of the circulating lymphocyte in healthy people showed variation during the day. An experimental animal study on the subject was carried out 60 years ago (27). In this study, in animals injected with endotoxin, toxin sensitivity was determined to be related to time-of-day. Recently, regulation of proinflammatory cytokine activity has attracted attention as one of the important links regarding the relationship between biological clocks and immune function. In macrophages stimulated by endotoxin, the increase in tumor necrosis factor (TNF)-α secretion may cause a change in the circadian rhythm depending on the endotoxin administration time (28). It is thought that there is a feedback mechanism between the formation of inflammation and the integration of the molecular

clock. Confirming this situation, BMAL1, CLOCK and Rev-Erb-α protein levels in cells decrease significantly after endotoxin injection, which is estimated to impair clock function (29-31). However, herpes virus infection induces BMAL1 promoter activity and results in a corresponding suppression of Cry1 and disruption in the feedback mechanism of the clock (32). All these data indicate that the circadian clock is affected in case of acute infection. However, the same is true for chronic infection as well. Significant changes occur in the immune system due to loss of function and mutations in genes associated with circadian rhythm (Table I).

Table I. Specific samples of altered adaptive immune phenotype in circadian mutant mice (Adapted from ref. 82)

Gene	Deletion	Adaptive immune phenotype	Ref.
Bmal1	Myeloid	Exacerbation of EAE symptoms	83
	CD4+ T cells	Loss of diurnal variation in EAE	84
Nr1d1	Global	Exacerbation of EAE symptoms	85
Ror-α$^{sg/sg}$	Global	Impaired Th17 cell development	28
Ror-γ	Global	Impaired Th17 cell development	36
Ror-α/γ	Global	No Th17 cell population Mice are resistant to EAE	28
Cry1/Cry2	Global	Mice are resistant to EAE	28
		Increased antibody-induced arthritis severity	86

The functioning of myeloid and lymphocyte subsets in both healthy humans and mice is another immune function related to the circadian rhythm (33). It is stated that variants of the clock gene Ror-γ and Ror-γt are important for the development of T helper (Th)17 cells, type 3 innate lymphoid cells, and lymphoid tissue inducer cells (34, 35). Ror-α, A canonical clock gene, is important for differentiation of the type 2 innate lymphoid cells (ILC2), which play a role in defense against allergy, type II inflammation, and parasitic infestations (35). Ror-α also has a role in the full development of Th17 cells (36). A disruption of molecular clock function can lead to abnormal Th17 cell development. Mice with impaired Th17 regulation become more susceptible to pathology in autoimmunity models such as experimental autoimmune encephalomyelitis (EAE, multiple sclerosis model) and colitis (37). Interestingly, Ror-γt mRNA expression is suppressed by melatonin, a hormone that is secreted from the pineal gland in a circadian rhythm and has a pleiotropic immunomodulatory effect (38). Recently, it has been discovered that circadian clocks also regulate neutrophil maturation (39).

In case of acute or chronic stress, the essential neuroendocrine response is activation of the HPA axis. Regardless of stress, the HPA axis also has a circadian rhythm governed daily by the SCN (40). In HPA activation, the brainstem and limbic forebrain stimulate corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) secretion from neurosecretory neurons of the paraventricular nucleus of the hypothalamus (PVN) (41). As a result of the CRH secretion (partially with the involvement of AVP), adrenocorticotropin-releasing hormone (ACTH) is released from the anterior pituitary into the general circulation, leading to the secretion of glucocorticoids such as cortisol in humans and corticosterone in rodents from the cortex of the adrenal glands (42, 43). The circadian rhythms of glucocorticoids peak just before the onset of the active period, which is nocturnal for most rodent species and diurnal for humans (44). This rhythm encompasses a dynamic ultradian pattern for both ACTH and glucocorticoid secretion, driven by pituitary ACTH release and autocrine feedback of glucocorticoids (45-47). There is a bidirectional interaction between the HPA axis and the immune system (45) (Figure 2).

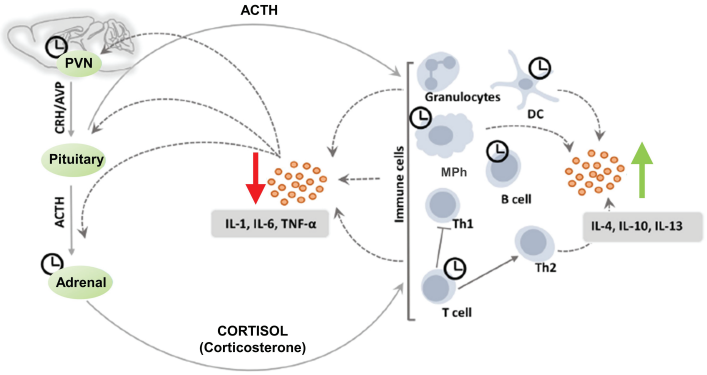

Figure 2. Circadian clocks in HPA axis-immune system crosstalk. Immune cells can activate the HPA axis via cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1 and IL-6 at the level of the paraventricular nucleus (PVN) of the hypothalamus as well as at the pituitary and adrenal, stimulating the secretion of glucocorticoids. Glucocorticoids in turn act on the receptors on the surface or in the cytoplasm of immune cells to suppress the induction of pro-inflammatory responses, and to promote a shift from T helper cell type 1 (Th1) toward Th2-mediated humoral immunity. This inhibits the production of pro-inflammatory cytokines, while promoting the production of anti-inflammatory cytokines, such as IL-4, IL-10 and IL-13 by various immune cells. In addition, ACTH/cortisol exerts direct anti-inflammatory and immune-modulating effects via the melanocortin system. CRH: corticotropin-releasing hormone, AVP: arginine vasopressin, DC: dendritic cell, MPh: macrophage (Modified from Ref. 42).

It is well known that immune cells can activate the HPA axis through cytokines such as tumor necrosis factor-alpha (TNF-α), interleukins (IL-1, IL-6) and type I interferons (IFNs) (48-51). Moreover, some cytokines can activate the HPA axis through different mechanisms (52, 53). It can also affect the viability and function of many immune cell types, including glucocorticoids, T cells, B cells, monocytes, macrophages, and granulocytes (54,55). Glucocorticoids suppress the synthesis and release of proinflammatory cytokines, thereby protect the host organism from the harmful consequences of prolonged hyperactivity of the immune system. Glucocorticoids are still the most widely used and most effective treatment to control allergic, autoimmune, inflammatory, and hematological disorders (56). Glucocorticoid receptors are found in almost all immune cells and affect proinflammatory regulators such as NF-κB (Nuclear Factor kappa B) and activator protein 1 (AP-1) by activating anti-inflammatory molecules such as glucocorticoid-induced-leucine zipper (GILZ), annexin-1, mitogen-inducible gene-6 (Mig-6), MAPK phosphatase-1 (MKP-1) and SLAP1 (SRC-like adaptor protein 1) (56-63). In contrast to the well-defined immunosuppressive effects of glucocorticoids, recent studies indicate that these hormones can have permissive and even stimulating effects on immune processes (64-67). It is suggested that acute stress enhances, while chronic stress suppresses the peripheral immune response, but the mechanism

of this dual role is still unknown (64).

The immune system-related cytokines, the number of hematopoietic cells, and the hormones interacting with the immune system in the blood show a circadian rhythm (68). These parameters oscillate according to activity or resting phase, depending on whether the species is diurnal (humans) or nocturnal (rodents). Both cellular and humoral components of the immune system show opposite rhythms in the blood. Although amount of hematopoietic stem cells, progenitor cells (HSPCs) and most mature leukocytes (excluding effector CD8+ T cells) decrease during the active period, they peak in circulation during the resting phase (night-time in humans and during the daytime period in rodents) (68, 69). Moreover, there is an increase in the release of mature immune cells and HSPCs from the bone marrow to the blood at the beginning of the resting period (69). This release pattern is associated with local sympathetic innervation, which mediates rhythmic down-regulation of the expression of CXC-chemokine ligand 12 (CXCL12; formerly known as SDF1), an important attachment factor for hematopoietic cells in the bone marrow. This release is dependent on local sympathetic innervation, which mediates rhythmic down-regulation of the expression of CXC-chemokine ligand 12 (CXCL12; formerly known as SDF1), an important retention factor for hematopoietic cells in the bone marrow. Therefore, at the onset of the active period, there is an increase in the levels of glucocorticoids (cortisol in humans and corticosterone in mice), epinephrine, norepinephrine, and proinflammatory cytokines such as TNF- α and IL-1β (31, 68, 70).

IMMUNE SYSTEM-RELATED DISEASES WITH SYMPTOMS IN A CIRCADIAN RHYTHM

Changes related to the circadian rhythm in the symptoms of common immune system-related diseases are summarized in Table II.

Table II. Effects of circadian rhythm on symptoms of immune system-related diseases (Adapted from Ref. 87).

Species	Disease	Oscillating parameter	Acrophase	Ref.
Human	Allergic rhinitis	Sneezing, nasal congestion	CT6	88
	Bronchial asthma	Broncho- constriction	CT6	88
		Sputum eosinophils, IL-5	CT7	89
	Ischemic stroke	Hypertension	CT6-12	73
	Myocardial infarction	Pain	CT9	74
	Rheumatoid arthritis	Stiffness, Pain, TNF, IL-6	CT5-8	71
	Sickle cell vaso-occlusive crisis	Hospital admission	CT18	90
Note: CT: actual circadian time in hours (e.g. CT6 = 6AM).				

In patients with rheumatoid arthritis, pain and stiffness in the joint regions are common, especially during the early morning hours, associated with the increase in TNF and IL-6 in the blood (71). In this disease, symptoms that increase in the morning are positively correlated with high levels of circulating proinflammatory cytokines. In addition, circadian changes are observed in circulating inflammatory metabolites. Experimentally, animals lacking a functional clock gene (Cry1–/– Cry2–/– mice) have a more pronounced phenotype in a collagen antibody-driven model of inflammatory arthritis (72). The risk of stroke and myocardial infarction is again at the peak level in the early morning hours compared to other time periods of the day (73, 74). The increased activity of the sympathetic nervous system during the early morning hours and thus the increase in blood pressure, as well as the increase in blood viscosity and coagulation, and thus the tendency to thrombosis, are responsible for this increased risk (75). In our study on the subject, we determined that circadian rhythm proteins directly affect the brain damage that develops after cerebral ischemia. We observed an increase in the levels of Bmal1, Per1, CLOCK circadian rhythm proteins and p-AKT and p-Erk-1/2 mediated neuronal survival. We also observed a decrease in the number of apoptotic cells in mice with midnight ischemic stroke (Zeitgeber 18; 24:00) compared to mice with morning stroke (Zeitgeber 0, 06:00). As a result of our proteomic analysis, although GNAZ, NEGR1, IMPCT and PDE1B levels increased, CSKP, HBB1, HBB2 and HBA levels were significantly decreased in Zeitgeber 18 group compared to morning Zeitgeber 0. The results of our study showed that neuronal damage was less in those that had ischemic stroke at night, and this was provided by increased expression of survival kinases and circadian rhythm-related proteins (76). In addition, regarding stroke, it can be said that the process that started with the release of peroxiredoxins from the cytosolic antioxidant proteins of ischemic cells in the brain turned into a different situation. These antioxidant proteins are among the conserved markers of circadian rhythms that are vital for redox balance. Peroxiredoxins can bind to TLR2 and TLR4 on macrophages infiltrating the brain. This binding triggers the activity of T cells such as IL-17 and IL-23 and thus aggravates brain damage (77). It has been suggested that in addition to the increased risk of morning myocardial infarction, the infarct sizes are also larger, and rhythmic leukocyte infiltration may be responsible for this situation (78). It is well known that the symptoms of asthma, a pulmonary inflammatory disease, vary throughout the day (79). Asthma symptoms become more pronounced at night due to circadian variation in lung function. The cause of circadian oscillations in inflammatory cell numbers in the asthmatic lung is unclear. However, murine studies show that BMAL1 deletion in myeloid cells increases eosinophil release in the ovalbumin model of allergic asthma. This evidence indicates that the biological clock in myeloid cells plays a role in this process (80). The pathological course of multiple sclerosis may vary depending on circadian and seasonal cycles. It has been suggested that relapses of the disease occur more frequently in spring and summer, and this is due to lower levels of melatonin, a hormone associated with circadian rhythm (81). There are also circadian rhythm-related changes in the EAE model of multiple sclerosis and T cell-mediated autoimmune disease.

CONCLUSION

The immune system has an important function that controls all body cells. The cooperation of the immune system with the nervous system and endocrine system is important to maintain homeostasis. The most important factors that threaten homeostasis are the environmental factors. Therefore, the adaptation capacity of the organism to environmental conditions is critical. One of the important mechanisms that provide this is the biological clocks in the body. Thus, the adaptation of the organism to circadian and seasonal rhythms is ensured. It is well known that body functions and immune activity change, especially depending on seasonal changes. However, it is also same for the circadian rhythm, but the relationship among immune activity, HPA axis, and circadian rhythm is not well known. However, the immune system shows circadian variations, including innate and adaptive immune activity. A prominent link between the biological clocks and the immune system is the regulation of proinflammatory cytokine production. There is a feedback mechanism between inflammation and the integration of the molecular clock. In relation to this situation, BMAL1, Rev-Erb-α and CLOCK protein levels in cells decrease significantly after endotoxin injection, which is predicted to impair clock function. The immune system-related cytokines, the number of hematopoietic cells, and the hormones interacting with the immune system in the blood have a circadian rhythm.

Pain and stiffness in the joints are common in patients with rheumatoid arthritis, especially during the early morning hours. In this disease, symptoms that increase in the morning are positively correlated with increased levels of circulating proinflammatory cytokines. The risk of stroke and myocardial infarction is higher during the early morning hours than at other time periods of the day. In our previous study, we determined that circadian rhythm proteins directly affect the brain damage that develops after cerebral ischemia. Furthermore, we observed that neuronal damage was less in those who had ischemic stroke at night and that the expression of survival kinases and circadian rhythm-related proteins played a role regarding to this situation. It is a phenomenon that is considered to have a higher risk of morning myocardial infarction. There are several studies showing that asthma symptoms vary daily and are more severe, especially during the early morning hours. In addition, the pathological course of multiple sclerosis can vary depending on circadian and seasonal cycles, and it is an important data on the relationship with the circadian rhythm, where relapses of this disease occur more frequently in spring and summer. Data on circadian rhythm and immune system physiology are important in terms of understanding the pathophysiology of immune system-related diseases and producing effective treatment strategies.

Conflict of interest:
Authors declare that there is no conflict of interest.

Financial conflict of interest:
Authors declare that they did not receive any financial support in this study.

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