Physiology and Pharmacology 28 (2024) 237-256
Review Article

Circadian rhythm and body health: A review of the literature

Shahrzad Sadat Eftekhar Vaghefi[1,2,3,4,5+], Reza Malekpour Afshar[1+], Fatemeh Shahsavari[7,5], Fatemeh Mousavi[4], Seyed Hossein Eftekhar Vaghefi[1], Seyyed Jafar Nosratabadi[2], Mohammad Khaksari[3], Zahra Soltani[3], Gholamreza Asadikaram[6], Manzoomeh Shamsi Meymandi[1], Alireza Raji Amir Hasani[3], Mona Saheli[8], Masoumeh Baghalishahi[8], Maryam Fekri Soofi Abadi[1], Mahnaz Mohammadizadeh[1], Shahriar Dabiri[1*]

1. Pathology and stem cell Research center, Kerman University of Medical, Sciences, Kerman, Iran
2. Department of Basic Sciences, Faculty of Medicine, Kerman Branch, Islamic Azad University, Kerman, Iran
3. Department of Physiology and Pharmacology, Kerman University of Medical Sciences, Kerman, Iran
4. Physiology Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
5. Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
6. Department of Biochemistry, School of Medicine, Kerman University of Medical Sciences, Kerman, Iran
7. Department of Biology, Faculty of Science, Shahid Bahonar University of Kerman, Kerman, Iran
8. Department of Anatomical Sciences, Kerman University of Medical Sciences, Kerman, Iran

ABSTRACT

Circadian rhythm is a biological clock that regulates various physiological and pathological processes in the body. It is believed that any disturbance in circadian rhythm leads to impairment in some physiological systems, such as the endocrine, reproductive, renal, and cardiovascular systems. Various internal and external factors can alter circadian homeostasis and metabolism in a tissue-specific manner, and any disruption in these temporal interactions can result in the development of some chronic disorders. Circadian rhythm plays a crucial role in the pathogenesis of diseases, including cardiovascular disease, neurodegenerative disease, mood disorders, sleep disorders, diabetes mellitus, metabolism disorders, and cancer. This review aims to provide a brief overview of the basic circadian processes and an overview of current and future research directions in circadian rhythm and its related treatments.

Keywords:
Circadian rhythm
Physiology
Circadian Clock System
Chronotherapy
Circadian disruption

Introduction

Overview of the circadian rhythm

- Definition of circadian rhythms

The human body follows a natural circadian rhythm (CR) clock. According to Merriam-Webster (1959), circadian rhythms refer to the natural cycle of physical, mental, and behavioral changes that occur in a 24-hour cycle or period (day/night cycles) (Chang et al., 2015).

* Corresponding author: Shahriar Dabiri, sh_dabiri@kmu.ac.ir
+These two authors contributed equally to this article.
Received 15 November 2023; Revised from 10 March 2024; Accepted 2 April 2024

Citation: Eftekhar Vaghefi S.S., Malekpour Afshar R, Shahsavari F, Mousavi F, Eftekhar Vaghefi S.H., Nosratabadi S.J., Khaksari M, Soltani Z, Asadikaram G, Shamsi Meymandi M, Raji Amir Hasani A, Saheli M, Baghalishahi M, Fekri Soofi Abadi M, Mohammadizadeh M, Dabiri S. Circadian rhythm and body health: A review of the literature. Physiology and Pharmacology 2024; 28: 237-256. http://dx.doi.org/10.61186/phypha.28.3.237

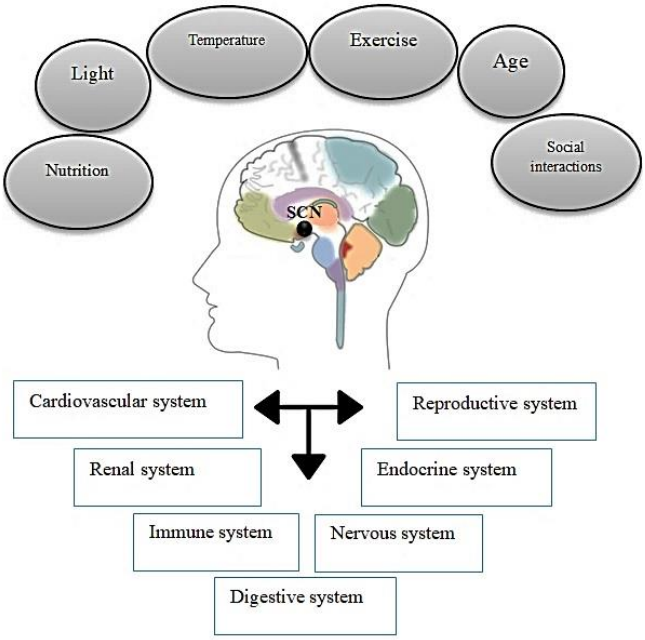

FIGURE 1. The suprachiasmatic nucleus (SCN), as a master regulator of the circadian system in the hypothalamus, receives internal and external signals and synchronizes peripheral clocks in various physiological systems.

These rhythms are found in all tissues of the mammalian body, and in addition, about 40% of protein-coding genes show oscillatory expression (Ruben et al., 2018). Furthermore, these rhythms regulate various biological and physiological processes of the body in living organisms including sleep and wake cycles (Liu et al., 2022), heart rate, arterial blood pressure (Jiang et al., 2019), body temperature (López-Olmeda 2017; Refinetti 2020), hormone production and secretion (Tsang et al., 2016), metabolism and obesity (Sebti et al., 2022), mood and depression (Scott and McClung 2021), immune system functions (Cox et al., 2022), urine production (Ramsay and Zagorodnyuk 2023), digestive system (Segers and Depoortere 2021), skeletal muscles (Luo et al., 2022) and other essential body functions.

Circadian rhythms can be in some forms depending on their duration, including high-frequency cycles (such as discrete hormonal pulses throughout the day), diurnal cycles (such as patterns of activity and rest), and longer cycles lasting months or years (such as reproductive cycles in certain species) (Onishi et al., 2020). However, most biological rhythms operate on roughly 24-hour cycles.

- Regulation of circadian rhythms: the role of circadian clocks

The circadian rhythm is influenced by various external changes and factors such as exposure to light and food consumption (Wang et al., 2021), as well as internal factors and natural changes, such as genetics and age (Chen et al., 2016). Disturbances caused by jet lag and shift work can also negatively affect the health of the biological rhythm (Wang et al., 2021). Therefore, any disturbance in the rhythm can lead to various health problems, including sleep disorders, mood disorders, metabolic disorders, cardiovascular diseases, neurodegenerative diseases, diabetes, and cancer (Farhud and Aryan 2018) (Figure 1).

In addition, as the disturbance in the circadian clock increases the risk of disease, many diseases can also change the circadian rhythm. Circadian rhythm regulation is a complex process and is controlled by a set of different genetic, molecular, and neural mechanisms and processes (Patke et al., 2020).

The circadian rhythm is controlled by the circadian clock. Circadian clocks are divided into two categories: central clock (suprachiasmatic nucleus- SCN) in the hypothalamus and peripheral clocks (non-SCN) in other organs in the body (Honma 2018). The SCN is the primary regulator and the main center of the circadian rhythms that communicate with other brain areas and sends numerous neurological and endocrine signals to peripheral tissues (Leembruggen et al., 2022). This nucleus synchronizes the internal clock with external cues,

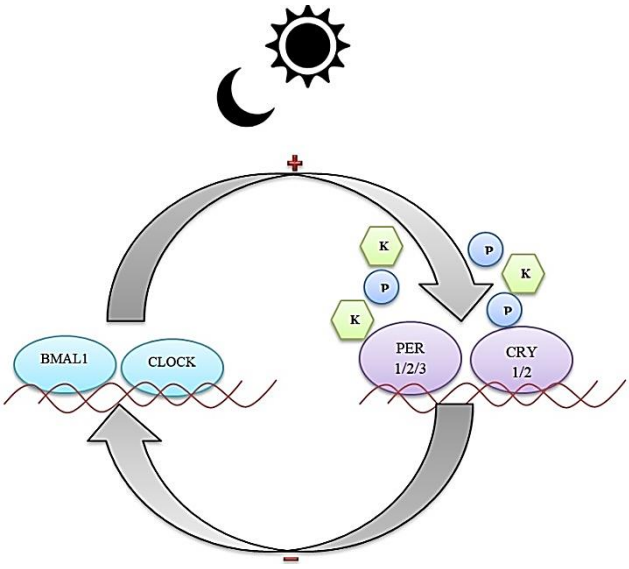

FIGURE 2. The molecular circadian network is formed from a feedback loop of CLOCK, BMAL, PERs, and CRYs elements, which lead to 24-hour rhythmic oscillations at target genes. K: kinase, P: phosphatase

such as light-dark cycles, and controls peripheral tissue clocks through the release of endogenous regulatory substances.

The SCN has an essential role in maintaining the systemic circadian rhythm and regulating downstream processes that affect metabolism, hormone secretion, and other physiological functions (Tarquini and Mazzoccoli 2017). Hormones such as melatonin, cortisol, and growth hormone also play an important role in circadian rhythm regulation and interact with the SCN and other brain regions (Ertosun et al., 2019). Light input is often used as the primary stimulus to transmit time signals from the SCN to peripheral clocks in other body cells (Alvord et al., 2022; Begemann et al., 2020; Míková et al., 2021).

Since the SCN can coordinate many behaviors, including feeding/ fasting, reproduction, and sleep-wake cycles, through the control of physiological fluctuations in metabolism, hormone levels, nutrition, and body temperature (Ono et al., 2023), it seems that any type of damage to this area can disrupt the mentioned functions (Gu et al., 2021). For example, it has been found that the destruction or removal of the SCN center of mice leads to disruption of circadian rhythms related to glucose uptake and insulin sensitivity (Peng et al., 2022).

Besides the central clock, other regulators called peripheral circadian clocks exist in some organs such as the digestive system, skeletal muscles, pancreas, lungs, spleen, reproductive system, kidneys, thymus, heart, prostate, liver, intestines, lymphocytes, skin, olfactory bulb and esophagus (Reddy et al., 2023; Zhang et al., 2020). There are many approaches in which these secondary or peripheral oscillators communicate with one another. For instance, by reacting to signals sent by the SCN or by receiving inputs directly and indirectly from the nervous system, such as hormonal, physiological, and other behavioral rhythms (Schibler et al., 2015; Walker et al., 2020). Autonomic nerves, local signals, and endocrine signaling are only some factors that influence the pattern of gene expression of peripheral tissues (Xie et al., 2019).

Unlike the central circadian clock (SCN), which only has independent oscillations, peripheral clocks do not have spontaneous oscillations and are often controlled by the oscillations of the main pacemaker (SCN) (Husse et al., 2014). There is a complex relationship between the SCN and surrounding tissues, and the maintenance of circadian rhythms in peripheral tissues is based on the individual needs of each tissue (Crislip et al., 2018; Gamble et al., 2014).

** Circadian clock genes*

At the molecular level, the SCN, as a molecular clock, regulates the 24-hour rhythmic expression of nuclear clock components through the bidirectional interaction of a main two-loop transcriptional-translational feedback loop (TTFL) (Anna and Kannan 2021). These positive and negative molecular feedback loops include

two activators (CLOCK and BMAL1) and two repressors (homologous circadian protein; PER1 and PER2), which are regulated through kinases and phosphatases and can be activated and inhibited together (Gul et al., 2020) (Figure 2).

The expression of clock genes within a cell can affect several signaling pathways that enable the cell to detect the time of day and carry out the proper functions. Therefore, feedback loops determine the timing of certain physiological functions and behaviors, such as sleep-wake cycles, stress, metabolism, and immune responses. The existence of circadian rhythms in both nucleated and non-nucleated cells indicates that the molecular clock is autonomous and can regulate itself using outside cues.

The PER1/ PER2/ PER3, BMAL1/ BMAL2, CRY1/ CRY2, and CLOCK genes are called "clock-controlled genes" and regulate translation and transcription processes (Luo et al., 2016). In some organs, such as kidney, liver, lung, and heart tissues, some rhythms are directly stimulated and activated by clock genes and operate independently of suprachiasmatic nucleus rhythms (Ono et al., 2023; Sahar and Sassone-Corsi 2012).

Brain and muscle aryl-hydrocarbon receptor nuclear translocator-like protein1 (BMAL1) gene

Circadian rhythmicity is entirely lost following the knockout (KO) of Bmal1. For example, The Bmal1- KO mice have a shorter lifespan and lower blood pressure than wild-type mice. In addition, they are also infertile and exhibit a circadian rhythmicity in their blood pressure and heart rate (Solocinski and Gumz 2015). Bmal1 KO results in a disruption in the circadian cycle under constant dark/ light conditions (Izumo et al., 2014).

Bmal1 is crucial for the ovarian steroidogenic cells' molecular clock, progesterone synthesis, and other processes related to female reproduction, and any disruption of the Bmal1 gene is sufficient to disrupt the reproductive cycle (Boden et al., 2013; Boden et al., 2010; Liu et al., 2014). In addition, mice lacking specific Bmal1 have shown defective insulin secretion and this is mainly due to impaired insulin secretion (de Jesus et al., 2022; Ye et al., 2020). Bmal1 KO animals are obese and exhibit patterns of food malabsorption, hyperlipidemia, and increased body weight (Richards and Gumz 2013). Telomerase Reverse Transcriptase transcription (TERT, a downstream gene of Bmal1) was boosted when the central clock protein Bmal1 was eliminated, while the overexpression of TERT promotes the growth of tumors (Tang et al., 2017). Circadian disruption induces Bmal1 downregulation, which produces osteoclasts and inhibition of bone production (osteogenesis), and leads to abnormal growth of the lower jaw (Zhou et al., 2018).

Period Circadian Regulator (PER) genes

The Per1, 2, and 3 genes are circadian protein homologs and are classified as part of a group of circadian clock genes that function as transcriptional repressors (Cao et al., 2023).

Per1 gene is related to cell proliferation and apoptosis and it has a significant impact on the development of oral, prostate, colon, breast, and ovarian cancers (Chen et al., 2021; Han et al., 2016; Lan et al., 2020; Li et al., 2016; Liu et al., 2021; Wang et al., 2015b). Per1 is now known to have a vital role in controlling the female sex's ability to produce progesterone (Zhang et al., 2019), so knocked out of the Per1 gene reduced the expression of progesterone receptor-related genes (Chen et al., 2021; Zhang et al., 2019).

Per2 is also involved in cell differentiation and proliferation and has been implicated in mammary epithelium and milk duct morphology and breast cancer (Wang et al., 2015a). The abnormal expression of Per2 increases the progression of oral squamous cell carcinoma (Guo et al., 2020). Per2 seems to have a role in neurodegenerative diseases and cognitive impairment patients (Bessi et al., 2020).

Because of their short half-life, Per1, 2 genes are ideal options for performing circadian rhythms. It has been discovered that mice with mutant Per2 and Per1 genes exhibit different responses to light. Also, the mutation in these two genes leads to premature aging (Zhang et al., 2019).

Per3 is crucial in the early development of the mouse cerebral cortex (Noda et al., 2019), gastrointestinal functions (Hoogerwerf 2010), prostate cancer (Hinoura et al., 2021), the regulation of metabolism and obesity (Peng et al., 2021).

Circadian locomotor output cycles kaput (Clock) gene

The clock mutant mouse (Δ19) was one of the first experimental models that demonstrated the significance of the circadian clock in metabolism. These animals (Δ19) demonstrate obesity and metabolic syndrome pheno-

type. It's interesting to note that, despite Clock mutant mice having normal activity rhythms in light/dark cycles; feeding behavior is disrupted and leads to obesity and endocrine disturbance (Turek et al., 2005).

Clock/Clock mutant mice have differences in pregnancy, severe birth defects, morphological deformity, and reduction of estradiol and progesterone serum levels (Miller and Takahashi 2013; Pilorz et al., 2018). Clock mutant mice do not have significant amounts of prolactin and secrete less milk than wild-type mice (Miller and Takahashi 2013).

In addition, the clock gene can be a desirable binding components in spermatogenesis or sperm production (Yang et al., 2018). The Clock is involved in the male reproductive system and may be important for future research into the relationship between spermatogenesis and circadian clock genes (He et al., 2023). Moreover, Clock expression influences cell growth and apoptosis-related genes in glioma cells (Wang et al., 2016). The Clock gene in human placenta tissue through hypoxia participates in the pathogenesis of preeclampsia (Li et al., 2020). A study by Borengasser et al. showed obesity can disrupt clock gene rhythmicity. They also found that maternal obesity disrupts the Clock gene and leads to metabolic programming of the liver in rat offspring (Borengasser et al., 2014).

Cryptochrome (CRY) gene

CRY1/ CRY2 have a significant role and importance in maintaining the circadian rhythmic state (Tokuoka et al., 2017). Cry1 encodes transcription factors that control the circadian clock in mammals and are expressed in many tissues and cells (Miller et al., 2020). In addition, Cry1 controls the repair of DNA damage, cell growth, and several other biological processes (Shafi et al., 2021). Cry1 can stop preimplantation meiosis and oocyte development in female mice (Guan et al., 2023). In males, Cry1 is primarily responsible for proper growth and normal function of the testis (Li et al., 2018).

The Cry2 gene is also involved in stress-depressive behaviors (Sokolowska et al., 2021), Cognitive dysfunctions (De Bundel et al., 2013), osteoarthritis (Bekki et al., 2020), Colorectal and breast cancers (Fang et al., 2015; Mao et al., 2015). Cry1 has a role in Hyperglycemia and diabetes (Kim et al., 2022; Tong et al., 2017). Rat liver cells treated with synthetic Cry1/2 agonists demonstrate enhanced glucose synthesis as a result of Cry1/2 activity (Hirota et al., 2012).

** Factors affecting the circadian rhythm:*

Various internal and external factors influence circadian rhythms, such as melatonin, light exposure, temperature, nutrition, age, physical activity, and social interactions.

Light

Most living organisms receive the time information necessary to reset their internal clocks through changes in light intensity throughout the day. Thus, light is frequently used as a stimulus in chronobiology studies to start clock-related reactions (Rivas et al., 2018).

Circadian clock regulation through light involves a signaling chain. Optical information is received by peroxisome proliferator-activated receptors (pRGCs), which then transmit it, directly to the SCN via the retino-hypothalamic tract (RHT) (Lokshin et al., 2015). This process regulates peripheral clocks through the SCN and the secretion of neurohumoral factors. When the SCN is stimulated by light, Ca2+ enters the cell; the intracellular signaling chain is activated and increases the expression of period genes which control the molecular clock (Walker et al., 2020). As light can provide precise synchronization with the environment, on the other hand, inappropriate exposure to light disrupts these rhythms and, as a result, can disrupt the downstream regulation of circadian rhythms in environmental systems (Meléndez-Fernández et al., 2023). For example, the circadian system controls glucocorticoid secretion from the adrenal glands, with peak concentrations in the morning that decline during the day in diurnal animals and humans (Focke and Iremonger 2020; Jha et al., 2021; Russell et al., 2015).

Temperature

Temperature has less effect on synchronization than light, making it a non-photic synchronizer. It's important to note that while cells and tissues outside of the SCN can synchronize with temperature changes, the SCN clock isn't responsive to temperature stimuli (Xie et al., 2019). The temperature of the house and the environment affect the metabolic rhythm of the body (McKie et al., 2019) and the secretion of glucocorticoids caused by stress and temperature (de Bruijn and Romero 2018). It has been reported that the circadian clock can be reset

by multiple cues, such as light, food, and temperature. The interplay between temperature and nutrition leads to metabolic disorders (Xie et al., 2019).

Scientists by examining the temperatures of 20-21°C (cool temperature) and 30°C (warm temperature), the range of 25.5- 27.6°C was suggested as the optimal temperature of the environment for the proper functioning of circadian rhythms in mice (Keijer et al., 2019). Mice exposed to temperatures of 30°C develop non-alcoholic fatty liver disease more frequently, and this is correlated with higher expression of genes related to fatty acid oxidation and lipid metabolism (Giles et al., 2017). It is interesting to note that some researchers have shown that the gender differences of mice affect how they react to the ambient temperature (Raun et al., 2020).

Melatonin

Melatonin is a hormone that is secreted by the pineal gland during the dark hours of the day. It plays a crucial role in coordinating the central and peripheral clock and is closely regulated by SCN neurons in response to light exposure (Meneses-Santos et al., 2018).

Melatonin is involved in various processes such as autophagy, apoptosis, cancer (Mehrzadi et al., 2021), ovulation, pregnancy, and childbirth (Olcese 2020; Talpur et al., 2018). Both the mother and fetus need to have melatonin for the development of a circadian rhythm. This hormone helps protect the fetus from metabolic pressures and supports the development of the nervous system and endocrine glands. Melatonin is also used to treat sleep problems and seasonal affective disorder and is a vital component of epilepsy treatment (Alston et al., 2019). Additionally, it regulates endocrine changes during the day and helps the body respond to daily changes (Dardente 2012). Melatonin deficiency has been linked to an increased risk of breast, colon, and rectal cancer (Rondanelli et al., 2013).

Nutrition (feeding)

Food, as a non-photic trigger, can directly affect circadian rhythms. It provides periodic access to various macronutrients that circulate in peripheral tissues (Xie et al., 2019).

Any changes in dietary patterns can disturb circadian clock homeostasis, and lead to endocrine and metabolic disorders (Mukherji et al., 2015). For example, a high-fat diet can reduce the intensity of circadian oscillations in the liver by affecting both the central and peripheral clock. This impact appears to be due to metabolic changes, blood glucose levels, and insulin resistance (Ding et al., 2022).

Furthermore, the composition and timing of food intake can influence the peripheral tissue clock, including the liver clock(Tahara and Shibata 2016). For example, Caffeine exerts a significant influence on the gene expression of peripheral tissue clocks in mice (Sherman et al., 2011) and can impact the body's circadian rhythm, clock, and sleep gene expression post-jet lag (Burke et al., 2015). Dietary polyphenols (Liu et al., 2023) and dietary polyamines (Li et al., 2019) also have an impact on the circadian system in organisms.

The timing of food intake significantly impacts the body's internal clock, influencing microbiota balance, intestinal activity, and nutrient uptake (Brooks et al., 2021; Zheng et al., 2020). Thus, increased cooperation and further studies involving chronobiologists and nutrition experts are essential to establish optimal meal timings and personalized dietary strategies. This approach aims to enhance bodily functions for individuals, ultimately lowering the risk of chronic illnesses.

Age

the probability of a decline in or loss of circadian rhythms increases with age (Deibel et al., 2015). These age-related disturbances in the circadian rhythm can contribute to the development of many aging-related diseases. Since the circadian clock regulates the sleep-wake cycle, it appears that the expression of these rhythms changes significantly with age (Mander et al., 2017; Shuboni-Mulligan et al., 2021). Older individuals may experience sleep problems, early morning awakenings, shorter total sleep time, and earlier sleep that can affect the start of the circadian rhythm and the speed of shifting the circadian phases (Duffy et al., 2015; Masuda et al., 2023; Shuboni-Mulligan et al., 2021). Studies have shown that older adults are more vulnerable to circadian changes than younger adults. Additionally, sleep termination is stabilized within a narrower range of circadian times in older adults, indicating a decrease in the circadian tendency to sleep in the early morning (Duffy et al., 2015).

On the other hand, the timing of the circadian rhythm of core body temperature changes with age, and these individuals become more sensitive to disturbances in

time and weak circadian rhythms (Duffy et al., 2015; Martinez-Nicolas et al., 2018). In addition, the circadian phases of melatonin, as well as the timing of the cortisol rhythm, also change with age (Adamczak-Ratajczak et al., 2017; Duffy et al., 2015). Changes in pupil, lens, and retinal function have also been observed with age (Freund et al., 2011). For example, the transmission of short-wavelength light through the lens decreases with age (Daneault et al., 2012). Animal studies have shown that the expression of Per1, Bmal1, Per2, and Clock genes is altered in aged mice compared to young mice (Bonaconsa et al., 2014).

Arousal stimuli

Non-optical cues, such as social interaction, physical activity and exercise, and stress, can affect the circadian rhythm by acting as arousal stimuli. However, light has been found to have a more significant effect on the main clock in rats than on arousal stimuli.

Stress

available data indicate that stress can change peripheral oscillators in, e.g., the liver, kidney, and heart. Thus, it may cause an imbalance between physiological and behavioral processes (Ota et al., 2021). It has been shown that restraint stress (RS) can alter circadian gene expression in the bladder and cause nocturia via changes in voiding frequency and bladder capacity (Ihara et al., 2019). Daily abstinence stress for three days per week can increase the expression of the Per2 gene in the liver, kidney, and submandibular gland without affecting the main clock rhythm in the SCN (Tahara et al., 2015).

The data obtained so far indicate that while the SCN circadian clock is well protected against stressors such as restraint, the peripheral clocks in various tissues are affected (Ota et al., 2021). Exposing pregnant mice to chronic stress can result in persistent disruption of coordination between SCN neurons in their offspring (Yun et al., 2020). The impact of stress on these clocks may be related to the neuroendocrine stress systems, including the SAM (adrenaline, noradrenaline) and HPA (glucocorticoids) axes (Tahara et al., 2015). External stressors such as restraint or immobility can lead to increased ACTH/GC and blood pressure during the inactive phase of the animal, even when the HPA is not active (Ota et al., 2021).

Social interactions

Social interactions are a crucial non-photic component that influences the modulation of circadian rhythms. Social connection is a complex stimulus that may affect eating, sleeping, and wakefulness (Cambras et al., 2011). Studies have shown that any disturbance in human social programs leads to disruption of the sleep/wake cycle (Elkhatib Smidt et al., 2022; Foster et al., 2013). For example, isolating mice in individual cages or groups of 3-4 per cage affects spontaneous locomotor activity (SLA) rhythm and the SCN activity (Fernandes et al., 2021).

The serotonergic system is known to be involved in the social isolation phenomenon (Sargin et al., 2016). An experiment conducted to determine the effect of social interaction on circadian rhythms has shown that the need for social contact is more significant in young mice than in adult mice (Lee and Noh 2015). In addition, in rats that live together and interact, the stability of individual rhythm increases (Fukumitsu and Kuroda 2023; Hodges et al., 2018).

Physical activity and exercise

Regular exercise has similar effects to light stimulation on the circadian clock and sleep/wake cycle. It can increase daytime wakefulness and lead to better sleep at night (Aoyama and Shibata 2017; Healy et al., 2021). Exercise can also improve sleep quality by increasing the production and secretion of melatonin (Cai et al., 2014; Tse et al., 2022), reducing heart rate, and lowering blood pressure (Oh et al., 2016). Additionally, exercise stimulates the neuroendocrine system, regulates hormones, and re-synchronizes the circadian clock (Hower et al., 2018).

Exercise especially affects the circadian clock through its effects on skeletal muscles (Aoyama and Shibata 2017; Mayeuf-Louchart et al., 2015), which are closely associated with diseases like diabetes, cardiovascular disease, and cancer (Mayeuf-Louchart et al., 2015). The intensity and duration of exercise can play a role in how it affects the circadian clock (Lang et al., 2022; Lewis et al., 2018; Sellami et al., 2019). Interestingly, research indicates that there is no difference between persons who exercise in the morning and people who exercise in the evening regarding their physiological and behavioral performance (Saidi et al., 2021). Exercise and physical activity through cellular and signaling pathways

lead to changes in the expression of BMAL1, PER1/2, CLOCK, and CRY1/2 genes (Dyar et al., 2015; Healy et al., 2021; Small et al., 2020).

** Circadian rhythm and physiological systems*

Recently, there has been a lot of attention given to the biological clock due to its significant effects on the body's physiological systems when disrupted. When the light/dark cycle changes, the SCN clock promptly adjusts internal processes to ensure all clocks and clock-regulated processes are effectively synchronized with the new environment (Ramkisoensing and Meijer 2015). (Figure 3).

- Reproductive system

The circadian rhythms that are controlled by feedback loops in the SCN play a crucial role in regulating various aspects of reproductive biology. These include the estrous cycle, LH levels, ovulation, sperm production and maturation, embryo implantation, and fertility (Pan et al., 2020; Silva and Domínguez 2020; Zhang et al., 2016). Recent research has shown how the circadian rhythm affects fertility and the complex interaction among hormones, fertility, and the circadian clock (Sciarra et al., 2020). It has been observed that placental communication and fetal circadian signals are essential for a successful pregnancy, and any alteration to the body's natural rhythm can negatively impact pregnancy and fetal development (Miller and Takahashi 2013).

Certain circadian clock genes such as Per2, Clock, Bmal1, and Cry1 in tissues like the ovarian, fallopian tube, uterus, and placenta play a crucial role in pregnancy. Bmal1, in particular, is important in gonadal steroidogenesis, expression of related genes, fertility, and reproductive endocrinology. Studies have shown that impaired reproduction, impaired reproductive gametes, impaired hormone secretion, and impaired signaling of the hypothalamus-pituitary-gonadal (H-P-G) axis were observed in Bmal1-KO mice (Li et al., 2022).

Other studies have focused on the role of gonadotropin-releasing hormone (GnRH) on the reproductive clock (Ando et al., 2018; Piet 2023; Uenoyama and Tsukamura 2023). It was found that the transient expression of the dominant-negative Clock protein (Clock19) in GnRH-secreting cells temporarily decreased GnRH production. Consequently, it was concluded that the circadian clock in these cells is related to the fluctuating expression of the nuclear circadian gene (Chu et al., 2013; Ono et al., 2023; Richards and Gumz 2013).

- Cardiovascular system

The regulation of blood pressure (BP) is an active area of research, with a focus on the circadian clock in cardiovascular tissue, as it affects BP (Douma and Gumz 2018; Jiang et al., 2019). Throughout the day, blood pressure increases and decreases by approximately 10 percent at night (Agarwal 2010; Zhang et al., 2021). However, individuals with diabetes, hypertension, and chronic renal disease whose blood pressure does not decrease at night are at higher risk of cardiovascular problems (Richards and Gumz 2013). This suggests that unregulated sodium reabsorption may be involved in the nocturnal BP reduction, and treatment with diuretics or angiotensin receptor blockers can aid in improving this issue at night (Fukuda et al., 2011).

The impact of circadian clock proteins on blood pressure control is not entirely clear. Studies have shown that Clock-KO mice have higher blood pressure (Fukuda et al., 2011), while Per1-deficient rats have significantly lower blood pressure compared to wild-type rats (Stow et al., 2012). Cry1/2-KO mice exhibit salt-sensitive blood pressure due to increased aldosterone synthesis (Doi et al., 2010).

Despite the research conducted on circadian rhythm and its relationship with the cardiovascular system, there is still limited knowledge in this area. Hence, more studies are necessary to understand the link between the circadian rhythm and blood pressure control.

- Renal system

Several studies have demonstrated the impact of circadian rhythm on various renal functions, such as renal function, blood pressure, absorption, and excretion (Firsov and Bonny 2018; Mohandas et al., 2022; Zhang et al., 2021). Recently, numerous circadian rhythm-related genes expressed in the kidneys have been identified, suggesting their involvement in circadian regulation (Gumz 2016; Zietara et al., 2022). The circadian rhythm influences daily fluctuations in urine volume, electrolyte excretion (sodium, potassium, phosphate, and magnesium), urinary protein excretion (proteinuria), activity of the renin-angiotensin-aldosterone system (RAAS), renal blood flow, and glomerular filtration rate (GFR) (Firsov et al., 2012; Nakamoto et al., 2021; Solocinski

and Gumz 2015).

The different components of the nephron appear to have independent circadian functions, and the molecular clock in the kidney can regulate these functions. These components also work together to manage processes related to the renal system (Speed et al., 2018). For example, studies suggest that there is a reciprocal relationship between the glomerular and molecular clock mechanisms (Huang et al., 2013). Furthermore, the expression of the apical sodium-glucose transporter (SGLT1) and sodium-hydrogen exchanger (NHE3) in the proximal tubule (PT) seems to be regulated by the circadian clock (Pizarro et al., 2013). The Bmal1, Per1/2/3, and Cry 1/2 genes are expressed in a circadian rhythm in the distal convoluted tubule (DCT)/ connecting tubule (CNT) parts (Zuber et al., 2009). According to certain research, genes like Bmal1, Clock, Per1, and Cry 2 exhibit circadian variations in their expression over 48 hours in the kidney tissue of wild-type mice (Solocinski and Gumz 2015).

- *Endocrine system*

The maintenance of homeostasis and the ability to adapt to environmental changes or stressful conditions are dependent on the relationship between endocrine factors, the central nervous system, and peripheral organs. The time of day has a supportive and regulatory effect on these hormone-related mechanisms (Gamble et al., 2014; Tsang et al., 2014). It is very important to synchronize the endogenous circadian system with environmental and behavioral factors, as well as endocrine factors (Scheer et al., 2021).

Glucocorticoids, which are steroid hormones synthesized in the adrenal cortex, play a crucial role in regulating the peripheral clock and endocrine system. They act as anti-inflammatory mediators in response to stress, metabolism, and cardiovascular and nervous functions (Dumbell et al., 2016; Son et al., 2011). Cortisol levels in humans exhibit a clear circadian cycle, with its highest levels in the morning. The gradual increase in cortisol levels during the sleep stage prepares the body for the normal stress associated with waking and increases activity (Benz et al., 2019).

Research has shown that the control of glucose levels in the body varies depending on the time of day (Qian and Scheer 2016). In the morning, blood sugar levels increase in normal individuals, while it increases even more in patients with type 1 and type 2 diabetes. This is believed to be due to an increase in hepatic glucose production, which causes a corresponding rise in insulin levels. Insulin then helps regulate glucose levels by reducing hepatic glucose production (Mason et al., 2020; Peng et al., 2022).

Furthermore, research has shown that short-term high-fat diets disrupt circadian clock gene homeostasis in several tissues and cause subsequent metabolic disturbances. This suggests that circadian dyssynchrony can lead to endocrine and metabolic abnormalities (Pendergast et al., 2013).

* *Treatment options for circadian rhythm disorders*

Circadian rhythm issues can significantly impact daily activities and cause discomfort. The most commonly recommended treatments include healthy lifestyle changes (Farhud and Aryan 2018) and chronotherapy (Ruan et al., 2021), often used together. (Figure 4).

1- Healthy lifestyle changes, such as maintaining a regular bedtime routine, avoiding daytime napping, engaging in physical activity and regular exercise, limiting caffeine, alcohol, nicotine, and certain drugs, managing exposure to light, and adhering to a regular meal plan, can all contribute to better sleep habits (Farhud and Aryan 2018).

2- In some cases, medication or nutritional supplements can be used to modify the sleep-wake cycle (Holst and Landolt 2018). Chronobiotics, a type of drug that directly affects the biological clock's output by modifying the circadian phase, represent a promising area of research for treating circadian disorders. These drugs must have no negative side effects(Huang et al., 2021). The term "chronobiotic" was first coined in the early 1970s to describe a medication that affects the physiological control of biological time structure (Cardinali et al., 2021a). Melatonin is the first and most well-known chronobiotic (Cruz-Sanabria et al., 2023). Other pharmaceuticals and dietary supplements, such as melatonin receptor agonists (Johnsa and Neville 2014), caffeine (Ruby et al., 2018), sleeping pills (Youn et al., 2020), and wakefulness-enhancing drugs (Engmann 2021) can also be used to manage sleep disorders.

3- Chronotherapy is a type of treatment that uses drugs by the body's natural circadian cycle to enhance their therapeutic effects while reducing any potential negative effects. It has been proven to be effective in treating sev-

eral diseases such as allergic rhinitis (Kudagammna and Vidanapathirana 2021), arthritis (Buttgereit et al., 2015), peptic ulcers (Singh et al., 2015) and cancer (Zhou et al., 2021). However, it is still not frequently employed in clinical practice (Petković et al., 2023).

Chronotherapy takes into account the patient's physiology and pathology and is performed in two ways: (1) by adjusting the sleep and wake rhythm of patients to prevent negative consequences and subsequent diseases, and (2) by considering the patient's circadian rhythm to improve treatment efficacy (Cardinali et al., 2021b).). Different types of chronotherapy include Bright light therapy (Lindskov et al., 2022), wake therapy/ sleep deprivation therapy (Guichard et al., 2021), sleep phase advance therapy (Takeshima et al., 2018), and triple chronotherapy (Webb 2022). Researches show that chronotherapy may be effective in the treatment of major depression, bipolar disorder, eating disorders, and delayed sleep phase disorders (Beauchamp and Lundgren 2016; Culnan et al., 2019; D'Agostino et al., 2020; Webb 2022). Overall, chronotherapy aims to regulate the output phase of circadian rhythms and the body's internal clock by ensuring adequate sleep, proper exposure to light, and the use of chronobiotic medications, such as melatonin.

- *The future of chronotherapy*

Recent studies on circadian rhythm and chronotherapy have made significant progress in our understanding of the importance of time in medical interventions, creating new opportunities for novel therapies (Yu et al., 2022). Understanding the relationship between our circadian rhythms can have a significant impact on how we approach medical treatments in our daily lives (Bhat et al., 2023).

One of the main challenges in using chronotherapy is the variability of internal clock timing among individuals, which can differ significantly across different phases (Kuo and Ladurner 2019). In addition, there are different chronotypes, whose physiological and behavioral rhythms are timed from early morning to late at night and are heavily influenced by the environment (Cardinali et al., 2021a). Therefore, it is important to explore new approaches in chronotherapy to determine each person's unique circadian rhythm.

Another obstacle to chronotherapy is the modern lifestyle, where people prefer street lights at night for safety reasons, and sleep is often viewed as a waste of time, leading to staying up late and waking up during the day (Cardinali et al., 2021a). These challenges can disrupt the biological cycles of individuals and increase the probability of developing diseases and disorders. Therefore, further research is required to better understand both current and novel therapies before implementing chronotherapy in clinical settings. Additionally, factors such as age, sex, and chronotype should also be taken into account when considering the use of chronotherapy.

Conclusion

Disruption of the circadian rhythm is a common problem in modern life. This is mostly caused by exposure to light at night, shift work, traveling, and lack of sleep. Therefore, it is crucial to understand the importance of maintaining a healthy circadian rhythm to improve overall health. Any disturbances in this delicate balance, whether caused by genetic factors or environmental factors, can have significant negative effects on health. These disturbances can increase the risk of chronic diseases such as obesity and diabetes, as well as sleep disorders, mood disorders, and physiological system disorders. Moreover, the circadian clock mechanisms and processes regulate a physiological/behavioral system that adapts to the 24-hour day-night cycles. It is essential to understand these basic circadian processes for the development of successful treatments in chronotherapy and its related domains.

Acknowledgments

The authors wish to thank the Kerman University of Medical Sciences for assisting in making this work possible.

Conflict of interest

The authors declare no conflicts of interest.

References

Adamczak-Ratajczak A, Kupsz J, Owecki M, Zielonka D, Sowinska A, Checinska-Maciejewska Z, et al. Circadian rhythms of melatonin and cortisol in manifest Huntington's disease and in acute cortical ischemic stroke. J Physiol Pharmacol 2017; 68: 539-546.

Agarwal R. Regulation of circadian blood pressure: from mice to astronauts. Curr Opin Nephrol Hypertens 2010; 19: 51-58. https://doi.org/10.1097/MNH.0b013e3283336ddb

Alston M, Cain S W, Rajaratnam S M W. Advances of melatonin-based therapies in the treatment of disturbed sleep and mood. Handb Exp Pharmacol 2019; 253: 305-319. https://doi.org/10.1007/164_2018_139

Alvord V M, Kantra E J, Pendergast J S. Estrogens and the circadian system. Semin Cell Dev Biol 2022; 126: 56-65. https://doi.org/10.1016/j.semcdb.2021.04.010

Ando H, Shahjahan M, Kitahashi T. Periodic regulation of expression of genes for kisspeptin, gonadotropin-inhibitory hormone and their receptors in the grass puffer: Implications in seasonal, daily and lunar rhythms of reproduction. Gen Comp Endocrinol 2018; 265: 149-153. https://doi.org/10.1016/j.ygcen.2018.04.006

Anna G, Kannan N N. Post-transcriptional modulators and mediators of the circadian clock. Chronobiol Int 2021; 38: 1244-1261. https://doi.org/10.1080/07420528.2021.1928159

Aoyama S, Shibata S. The role of circadian rhythms in muscular and osseous physiology and their regulation by nutrition and exercise. Front Neurosci 2017; 11: 63. https://doi.org/10.3389/fnins.2017.00063

Beauchamp M T, Lundgren J D. A systematic review of bright light therapy for eating disorders. The Primary Care Companion for CNS Disorders 2016; 18: 26718. https://doi.org/10.4088/PCC.16r02008

Begemann K, Neumann A M, Oster H. Regulation and function of extra-SCN circadian oscillators in the brain. Acta Physiol (Oxf) 2020; 229: e13446. https://doi.org/10.1111/apha.13446

Bekki H, Duffy T, Okubo N, Olmer M, Alvarez-Garcia O, Lamia K, et al. Suppression of circadian clock protein cryptochrome 2 promotes osteoarthritis. Osteoarthritis Cartilage 2020; 28: 966-976. https://doi.org/10.1016/j.joca.2020.04.004

Benz A, Meier M, Mankin M, Unternaehrer E, Pruessner J C. The duration of the cortisol awakening pulse exceeds sixty minutes in a meaningful pattern. Psychoneuroendocrinology 2019; 105: 187-194. https://doi.org/10.1016/j.psyneuen.2018.12.225

Bessi V, Balestrini J, Bagnoli S, Mazzeo S, Giacomucci G, Padiglioni S, et al. Influence of ApoE genotype and clock T3111C Interaction with cardiovascular risk factors on the progression to Alzheimer's disease in subjective cognitive decline and mild cognitive impairment patients. J Pers Med 2020; 10. https://doi.org/10.3390/jpm10020045

Bhat B B, Mehta C H, Suresh A, Velagacherla V, Nayak U Y. Controlled Release technologies for chronotherapy: current status and future perspectives. Curr Pharm Des 2023; 29: 1069-1091. https://doi.org/10.2174/1381612829666230423144232

Boden M J, Varcoe T J, Kennaway D J. Circadian regulation of reproduction: from gamete to offspring. Prog Biophys Mol Biol 2013; 113: 387-397. https://doi.org/10.1016/j.pbiomolbio.2013.01.003

Boden M J, Varcoe T J, Voultsios A, Kennaway D J. Reproductive biology of female Bmal1 null mice. Reproduction 2010; 139: 1077-1090. https://doi.org/10.1530/REP-09-0523

Bonaconsa M, Malpeli G, Montaruli A, Carandente F, Grassi-Zucconi G, Bentivoglio M. Differential modulation of clock gene expression in the suprachiasmatic nucleus, liver and heart of aged mice. Exp Gerontol 2014; 55: 70-79. https://doi.org/10.1016/j.exger.2014.03.011

Borengasser S J, Kang P, Faske J, Gomez-Acevedo H, Blackburn M L, Badger T M, et al. High fat diet and in utero exposure to maternal obesity disrupts circadian rhythm and leads to metabolic programming of liver in rat offspring. PLoS One 2014; 9: e84209. https://doi.org/10.1371/journal.pone.0084209

Brooks J F, 2nd, Behrendt C L, Ruhn K A, Lee S, Raj P, Takahashi J S, et al. The microbiota coordinates diurnal rhythms in innate immunity with the circadian clock. Cell 2021; 184: 4154-4167. https://doi.org/10.1016/j.cell.2021.07.001

Burke T M, Markwald R R, McHill A W, Chinoy E D, Snider J A, Bessman S C, et al. Effects of caffeine on the human circadian clock in vivo and in vitro. Sci Transl Med 2015; 7: 305ra146-305ra146. https://doi.org/10.1126/scitranslmed.aac5125

Buttgereit F, Smolen J S, Coogan A N, Cajochen C. Clocking in: chronobiology in rheumatoid arthritis. Nat Rev Rheumatol 2015; 11: 349-356. https://doi.org/10.1038/nrrheum.2015.31

Cai Z Y, Wen-Chyuan Chen K, Wen H J. Effects of a group-based step aerobics training on sleep quality and melatonin levels in sleep-impaired postmenopausal women. J Strength Cond Res 2014; 28: 2597-2603. https://doi.org/10.1519/JSC.0000000000000428

Cambras T, Castejón L, Díez-Noguera A. Social interaction and sex differences influence rat temperature circadian rhythm under LD cycles and constant light. Physiology & Behavior 2011; 103: 365-371. https://doi.org/10.1016/j.physbeh.2011.03.010

Cao X, Wang L, Selby C P, Lindsey-Boltz L A, Sancar A. Analysis of mammalian circadian clock protein complex-

es over a circadian cycle. J Biol Chem 2023; 299: 102929. https://doi.org/10.1016/j.jbc.2023.102929

Cardinali D P, Brown G M, Pandi-Perumal S R. Chapter 24 - Chronotherapy. In: Swaab DF, Kreier F, Lucassen PJ, Salehi A and Buijs RM, editors. Handbook of clinical neurology. Vol 179: Elsevier, 2021a: 357-370. https://doi.org/10.1016/B978-0-12-819975-6.00023-6

Cardinali D P, Brown G M, Pandi-Perumal S R. Chronotherapy. Handb Clin Neurol 2021b; 179: 357-370. https://doi.org/10.1016/B978-0-12-819975-6.00023-6

Chang Y G, Cohen S E, Phong C, Myers W K, Kim Y I, Tseng R, et al. Circadian rhythms. A protein fold switch joins the circadian oscillator to clock output in cyanobacteria. Science 2015; 349: 324-328. https://doi.org/10.1126/science.1260031

Chen C-Y, Logan R W, Ma T, Lewis D A, Tseng G C, Sibille E, et al. Effects of aging on circadian patterns of gene expression in the human prefrontal cortex. Proceedings of the National Academy of Sciences 2016; 113: 206-211. https://doi.org/10.1073/pnas.1508249112

Chen M, Zhang L, Liu X, Ma Z, Lv L. PER1 is a prognostic biomarker and correlated with immune infiltrates in ovarian cancer. Front Genet 2021; 12: 697471. https://doi.org/10.3389/fgene.2021.697471

Chu A, Zhu L, Blum I D, Mai O, Leliavski A, Fahrenkrug J, et al. Global but not gonadotrope-specific disruption of Bmal1 abolishes the luteinizing hormone surge without affecting ovulation. Endocrinology 2013; 154: 2924-2935. https://doi.org/10.1210/en.2013-1080

Cox S L, O'Siorain J R, Fagan L E, Curtis A M, Carroll R G. Intertwining roles of circadian and metabolic regulation of the innate immune response. Semin Immunopathol 2022; 44: 225-237. https://doi.org/10.1007/s00281-021-00905-5

Crislip G R, Masten S H, Gumz M L. Recent advances in understanding the circadian clock in renal physiology. Current Opinion in Physiology 2018; 5: 38-44. https://doi.org/10.1016/j.cophys.2018.06.002

Cruz-Sanabria F, Carmassi C, Bruno S, Bazzani A, Carli M, Scarselli M, et al. Melatonin as a chronobiotic with sleep-promoting properties. Curr Neuropharmacol 2023; 21: 951-987. https://doi.org/10.2174/1570159X20666220217152617

Culnan E, McCullough L M, Wyatt J K. Circadian rhythm sleep-wake phase disorders. Neurol Clin 2019; 37: 527-543. https://doi.org/10.1016/j.ncl.2019.04.003

D'Agostino A, Ferrara P, Terzoni S, Ostinelli E G, Carrara C, Prunas C, et al. Efficacy of Triple Chronotherapy in unipolar and bipolar depression: A systematic review of the available evidence. J Affect Disord 2020; 276: 297-304. https://doi.org/10.1016/j.jad.2020.07.026

Daneault V, Vandewalle G, Hébert M, Teikari P, Mure L S, Doyon J, et al. Does pupil constriction under blue and green monochromatic light exposure change with age? J Biol Rhythms 2012; 27: 257-264. https://doi.org/10.1177/0748730412441172

Dardente H. Melatonin-dependent timing of seasonal reproduction by the pars tuberalis: pivotal roles for long daylengths and thyroid hormones. J Neuroendocrinol 2012; 24: 249-266. https://doi.org/10.1111/j.1365-2826.2011.02250.x

de Bruijn R, Romero L M. The role of glucocorticoids in the vertebrate response to weather. Gen Comp Endocrinol 2018; 269: 11-32. https://doi.org/10.1016/j.ygcen.2018.07.007

De Bundel D, Gangarossa G, Biever A, Bonnefont X, Valjent E. Cognitive dysfunction, elevated anxiety, and reduced cocaine response in circadian clock-deficient cryptochrome knockout mice. Front Behav Neurosci 2013; 7: 152. https://doi.org/10.3389/fnbeh.2013.00152

de Jesus D S, Bargi-Souza P, Cruzat V, Yechoor V, Carpinelli A R, Peliciari-Garcia R A. BMAL1 modulates ROS generation and insulin secretion in pancreatic β-cells: An effect possibly mediated via NOX2. Mol Cell Endocrinol 2022; 555: 111725. https://doi.org/10.1016/j.mce.2022.111725

Deibel S H, Zelinski E L, Keeley R J, Kovalchuk O, McDonald R J. Epigenetic alterations in the suprachiasmatic nucleus and hippocampus contribute to age-related cognitive decline. Oncotarget 2015; 6: 23181-23203. https://doi.org/10.18632/oncotarget.4036

Ding L, Liu J, Zhou L, Jia X, Li S, Zhang Q, et al. A high-fat diet disrupts the hepatic and adipose circadian rhythms and modulates the diurnal rhythm of gut microbiota-derived short-chain fatty acids in gestational mice. Front Nutr 2022; 9: 925390. https://doi.org/10.3389/fnut.2022.925390

Doi M, Takahashi Y, Komatsu R, Yamazaki F, Yamada H, Haraguchi S, et al. Salt-sensitive hypertension in circadian clock-deficient Cry-null mice involves dysregulated adrenal Hsd3b6. Nat Med 2010; 16: 67-74. https://doi.org/10.1038/nm.2061

Douma L G, Gumz M L. Circadian clock-mediated regulation of blood pressure. Free Radic Biol Med 2018; 119: 108-114. https://doi.org/10.1016/j.freeradbiomed.2017.11.024

Duffy J F, Zitting K M, Chinoy E D. Aging and circadian rhythms. Sleep Med Clin 2015; 10: 423-434. https://doi.org/10.1016/j.jsmc.2015.08.002

Dumbell R, Matveeva O, Oster H. Circadian clocks, stress, and immunity. Front Endocrinol (Lausanne) 2016; 7: 37. https://doi.org/10.3389/fendo.2016.00037

Dyar K A, Ciciliot S, Tagliazucchi G M, Pallafacchina G, Tothova J, Argentini C, et al. The calcineurin-NFAT pathway controls activity-dependent circadian gene expression in slow skeletal muscle. Mol Metab 2015; 4: 823-833. https://doi.org/10.1016/j.molmet.2015.09.004

Elkhatib Smidt S D, Ghorai A, Taylor S C, Gehringer B N, Dow H C, Langer A, et al. The relationship between autism spectrum and sleep-wake traits. Autism Res 2022; 15: 641-652. https://doi.org/10.1002/aur.2660

Engmann O. How Psychoactive Drugs and the circadian clock are enlightening one another. Adv Exp Med Biol 2021; 1344: 129-152. https://doi.org/10.1007/978-3-030-81147-1_8

Ertosun M G, Kocak G, Ozes O N. The regulation of circadian clock by tumor necrosis factor alpha. Cytokine Growth Factor Rev 2019; 46: 10-16. https://doi.org/10.1016/j.cytogfr.2019.04.001

Fang L, Yang Z, Zhou J, Tung J Y, Hsiao C D, Wang L, et al. Circadian Clock Gene CRY2 Degradation Is Involved in Chemoresistance of Colorectal Cancer. Mol Cancer Ther 2015; 14: 1476-1487. https://doi.org/10.1158/1535-7163.MCT-15-0030

Farhud D, Aryan Z. Circadian rhythm, lifestyle and health: a narrative review. Iran J Public Health 2018; 47: 1068-1076.

Fernandes P, Pereira L M, Horta N A C, Cardoso T S R, Coimbra C C, Szawka R E, et al. Social interaction masking contributes to changes in the activity of the suprachiasmatic nucleus and impacts on circadian rhythms. Physiol Behav 2021; 237: 113420. https://doi.org/10.1016/j.physbeh.2021.113420

Firsov D, Bonny O. Circadian rhythms and the kidney. Nat Rev Nephrol 2018; 14: 626-635. https://doi.org/10.1038/s41581-018-0048-9

Firsov D, Tokonami N, Bonny O. Role of the renal circadian timing system in maintaining water and electrolytes homeostasis. Mol Cell Endocrinol 2012; 349: 51-55. https://doi.org/10.1016/j.mce.2011.06.037

Focke C M B, Iremonger K J. Rhythmicity matters: circadian and ultradian patterns of HPA axis activity. Mol Cell Endocrinol 2020; 501: 110652. https://doi.org/10.1016/j.mce.2019.110652

Foster R G, Peirson S N, Wulff K, Winnebeck E, Vetter C, Roenneberg T. Sleep and circadian rhythm disruption in social jetlag and mental illness. Prog Mol Biol Transl Sci 2013; 119: 325-346. https://doi.org/10.1016/B978-0-12-396971-2.00011-7

Freund P R, Watson J, Gilmour G S, Gaillard F, Sauvé Y. Differential changes in retina function with normal aging in humans. Doc Ophthalmol 2011; 122: 177-190. https://doi.org/10.1007/s10633-011-9273-2

Fukuda M, Wakamatsu-Yamanaka T, Mizuno M, Miura T, Tomonari T, Kato Y, et al. Angiotensin receptor blockers shift the circadian rhythm of blood pressure by suppressing tubular sodium reabsorption. Am J Physiol Renal Physiol 2011; 301: 953-957. https://doi.org/10.1152/ajprenal.00167.2011

Fukumitsu K, Kuroda K O. Behavioral and histochemical characterization of sexually dimorphic responses to acute social isolation and reunion in mice. Neurosci Res 2023; 194: 36-43. https://doi.org/10.1016/j.neures.2023.04.001

Gamble K L, Berry R, Frank S J, Young M E. Circadian clock control of endocrine factors. Nat Rev Endocrinol 2014; 10: 466-475. https://doi.org/10.1038/nrendo.2014.78

Giles D A, Moreno-Fernandez M E, Stankiewicz T E, Graspeuntner S, Cappelletti M, Wu D, et al. Thermoneutral housing exacerbates nonalcoholic fatty liver disease in mice and allows for sex-independent disease modeling. Nat Med 2017; 23: 829-838. https://doi.org/10.1038/nm.4346

Gu C, Li J, Zhou J, Yang H, Rohling J. Network Structure of the master clock is important for its primary function. Front Physiol 2021; 12: 678391. https://doi.org/10.3389/fphys.2021.678391

Guan Y, Xu M, Zhang Z, Liu C, Zhou J, Lin F, et al. Maternal circadian disruption before pregnancy impairs the ovarian function of female offspring in mice. Sci Total Environ 2023; 864: 161161. https://doi.org/10.1016/j.scitotenv.2022.161161

Guichard K, Micoulaud-Franchi J A, Philip P, Taillard J. Sleep deprivation therapy to reset the circadian pacemaker in a non-24-hour sleep-wake disorder: a case report. J Clin Sleep Med 2021; 17: 1503-1506. https://doi.org/10.5664/jcsm.9294

Gul S, Aydin C, Ozcan O, Gurkan B, Surme S, Baris I, et al. The Arg-293 of Cryptochrome1 is responsible for the allosteric regulation of CLOCK-CRY1 binding in circadian rhythm. J Biol Chem 2020; 295: 17187-17199. https://doi.org/10.1074/jbc.RA120.014333

Gumz M L. Molecular basis of circadian rhythmicity in renal physiology and pathophysiology. Exp Physiol 2016; 101: 1025-1029. https://doi.org/10.1113/EP085781

Guo F, Tang Q, Chen G, Sun J, Zhu J, Jia Y, et al. Aberrant expression and subcellular localization of PER2

promote the progression of oral squamous cell carcinoma. Biomed Res Int 2020; 2020: 8587458. https://doi.org/10.1155/2020/8587458

Han Y, Meng F, Venter J, Wu N, Wan Y, Standeford H, et al. miR-34a-dependent overexpression of Per1 decreases cholangiocarcinoma growth. J Hepatol 2016; 64: 1295-1304. https://doi.org/10.1016/j.jhep.2016.02.024

He M, Liu K, Cao J, Chen Q. An update on the role and potential mechanisms of clock genes regulating spermatogenesis: A systematic review of human and animal experimental studies. Rev Endocr Metab Disord 2023; 24: 585-610. https://doi.org/10.1007/s11154-022-09783-0

Healy K L, Morris A R, Liu A C. Circadian synchrony: sleep, nutrition, and physical activity. Front Netw Physiol 2021; 1. https://doi.org/10.3389/fnetp.2021.732243

Hinoura T, Mukai S, Kamoto T, Kuroda Y. PER3 polymorphisms and their association with prostate cancer risk in Japanese men. J Prev Med Hyg 2021; 62: 489-495.

Hirota T, Lee J W, St John P C, Sawa M, Iwaisako K, Noguchi T, et al. Identification of small molecule activators of cryptochrome. Science 2012; 337: 1094-1097. https://doi.org/10.1126/science.1223710

Hodges T E, Baumbach J L, McCormick C M. Predictors of social instability stress effects on social interaction and anxiety in adolescent male rats. Dev Psychobiol 2018; 60: 651-663. https://doi.org/10.1002/dev.21626

Holst S C, Landolt H P. Sleep-wake neurochemistry. Sleep Med Clin 2018; 13: 137-146. https://doi.org/10.1016/j.jsmc.2018.03.002

Honma S. The mammalian circadian system: a hierarchical multi-oscillator structure for generating circadian rhythm. J Physiol Sci 2018; 68: 207-219. https://doi.org/10.1007/s12576-018-0597-5

Hoogerwerf W A. Role of clock genes in gastrointestinal motility. Am J Physiol Gastrointest Liver Physiol 2010; 299: 549-555. https://doi.org/10.1152/ajpgi.00147.2010

Hower I M, Harper S A, Buford T W. Circadian rhythms, exercise, and cardiovascular health. J Circadian Rhythms 2018; 16: 7. https://doi.org/10.5334/jcr.164

Huang J Q, Lu M, Ho C T. Health benefits of dietary chronobiotics: beyond resynchronizing internal clocks. Food Funct 2021; 12: 6136-6156. https://doi.org/10.1039/D1FO00661D

Huang X M, Chen W L, Yuan J P, Yang Y H, Mei Q H, Huang L X. Altered diurnal variation and localization of clock proteins in the remnant kidney of 5/6 nephrectomy rats. Nephrology (Carlton) 2013; 18: 555-562. https://doi.org/10.1111/nep.12111

Husse J, Leliavski A, Tsang A H, Oster H, Eichele G. The light-dark cycle controls peripheral rhythmicity in mice with a genetically ablated suprachiasmatic nucleus clock. Faseb j 2014; 28: 4950-4960. https://doi.org/10.1096/fj.14-256594

Ihara T, Nakamura Y, Mitsui T, Tsuchiya S, Kanda M, Kira S, et al. Intermittent restraint stress induces circadian misalignment in the mouse bladder, leading to nocturia. Sci Rep 2019; 9: 10069. https://doi.org/10.1038/s41598-019-46517-w

Izumo M, Pejchal M, Schook A C, Lange R P, Walisser J A, Sato T R, et al. Differential effects of light and feeding on circadian organization of peripheral clocks in a forebrain Bmal1 mutant. eLife 2014; 3: e04617. https://doi.org/10.7554/eLife.04617

Jha P K, Bouâouda H, Kalsbeek A, Challet E. Distinct feedback actions of behavioural arousal to the master circadian clock in nocturnal and diurnal mammals. Neurosci Biobehav Rev 2021; 123: 48-60. https://doi.org/10.1016/j.neubiorev.2020.12.011

Jiang T T, Ji S, Yang G R, Chen L H. [Research advances in relationship between biological clock and cardiovascular diseases]. Sheng Li Xue Bao 2019; 71: 783-791.

Johnsa J D, Neville M W. Tasimelteon:A melatonin receptor agonist for non-24-hour sleep-wake disorder. Annals of Pharmacotherapy 2014; 48: 1636-1641. https://doi.org/10.1177/1060028014550476

Keijer J, Li M, Speakman J R. To best mimic human thermal conditions, mice should be housed slightly below thermoneutrality. Mol Metab 2019; 26: 4. https://doi.org/10.1016/j.molmet.2019.05.007

Kim Y Y, Jang H, Lee G, Jeon Y G, Sohn J H, Han J S, et al. Hepatic GSK3β-dependent CRY1 degradation contributes to diabetic hyperglycemia. Diabetes 2022; 71: 1373-1387. https://doi.org/10.2337/db21-0649

Kudagammna S T, Vidanapathirana G U. Chronobiology and chronotherapy of allergic diseases. Sri Lanka Journal of Child Health 2021; 50: 711-715. https://doi.org/10.4038/sljch.v50i4.9893

Kuo T T, Ladurner A G. Exploiting the circadian clock for improved cancer therapy: perspective from a cell biologist. Front Genet 2019; 10: 1210. https://doi.org/10.3389/fgene.2019.01210

Lan R, Jin B, Liu Y Z, Zhang K, Niu T, You Z. Genome and transcriptome profiling of FBXW family in human prostate cancer. Am J Clin Exp Urol 2020; 8: 116-128.

Lang C, Richardson C, Short M A, Gradisar M. Low-intensity scheduled morning exercise for adolescents with a late chronotype: a novel treatment to advance circadian phase? Sleep Adv 2022; 3: zpac021. https://doi.org/10.1093/sleepadvances/zpac021

Lee H, Noh J. Social exclusion intensifies anxiety-like behavior in adolescent rats. Behav Brain Res 2015; 284: 112-117. https://doi.org/10.1016/j.bbr.2015.02.006

Leembruggen A J L, Stamp L A, Bornstein J C, Hao M M. Circadian control of gastrointestinal motility. Adv Exp Med Biol 2022; 1383: 191-203. https://doi.org/10.1007/978-3-031-05843-1_18

Lewis P, Korf H W, Kuffer L, Groß J V, Erren T C. Exercise time cues (zeitgebers) for human circadian systems can foster health and improve performance: a systematic review. BMJ Open Sport Exerc Med 2018; 4: e000443. https://doi.org/10.1136/bmjsem-2018-000443

Li C, Xiao S, Hao J, Liao X, Li G. Cry1 deficiency leads to testicular dysfunction and altered expression of genes involved in cell communication, chromatin reorganization, spermatogenesis, and immune response in mouse testis. Mol Reprod Dev 2018; 85: 325-335. https://doi.org/10.1002/mrd.22968

Li H X, Fu X J, Yang K, Chen D, Tang H, Zhao Q. The clock gene PER1 suppresses expression of tumor-related genes in human oral squamous cell carcinoma. Oncotarget 2016; 7: 20574-20583. https://doi.org/10.18632/oncotarget.7827

Li J, Zhang L, Xiong J, Cheng X, Huang Y, Su Z, et al. Polyamines disrupt the KaiABC oscillator by inducing protein denaturation. Molecules 2019; 24. https://doi.org/10.3390/molecules24183351

Li T, Bai Y, Jiang Y, Jiang K, Tian Y, Gu J, et al. The potential impacts of circadian rhythm disturbances on male fertility. Front Endocrinol (Lausanne) 2022; 13: 1001316. https://doi.org/10.3389/fendo.2022.1001316

Li Y, Li J, Hou Y, Huang L, Bian Y, Song G, et al. Circadian clock gene clock is involved in the pathogenesis of preeclampsia through hypoxia. Life Sci 2020; 247: 117441. https://doi.org/10.1016/j.lfs.2020.117441

Lindskov F O, Iversen H K, West A S. Clinical outcomes of light therapy in hospitalized patients - A systematic review. Chronobiol Int 2022; 39: 299-310. https://doi.org/10.1080/07420528.2021.1993240

Liu C, Tang X, Gong Z, Zeng W, Hou Q, Lu R. Circadian rhythm sleep disorders: genetics, mechanisms, and adverse effects on health. Front Genet 2022; 13: 875342. https://doi.org/10.3389/fgene.2022.875342

Liu S, Cheng L, Liu Y, Zhan S, Wu Z, Zhang X. Relationship between dietary polyphenols and gut microbiota: new clues to improve cognitive disorders, Mood Disorders and Circadian Rhythms. Foods 2023; 12. https://doi.org/10.3390/foods12061309

Liu Y, Hao J, Yuan G, Wei M, Bu Y, Jin T, et al. PER1 as a tumor suppressor attenuated in the malignant phenotypes of breast cancer cells. Int J Gen Med 2021; 14: 7077-7087. https://doi.org/10.2147/IJGM.S328184

Liu Y, Johnson B P, Shen A L, Wallisser J A, Krentz K J, Moran S M, et al. Loss of BMAL1 in ovarian steroidogenic cells results in implantation failure in female mice. Proc Natl Acad Sci U S A 2014; 111: 14295-14300. https://doi.org/10.1073/pnas.1209249111

Lokshin M, LeSauter J, Silver R. Selective Distribution of Retinal Input to Mouse SCN Revealed in Analysis of Sagittal Sections. J Biol Rhythms 2015; 30: 251-257. https://doi.org/10.1177/0748730415584058

López-Olmeda J F. Nonphotic entrainment in fish. Comp Biochem Physiol A Mol Integr Physiol 2017; 203: 133-143. https://doi.org/10.1016/j.cbpa.2016.09.006

Luo W, Ma S, Yang Y, Wang C, Zhang D, Zhang Q, et al. TFEB regulates PER3 expression via glucose-dependent effects on CLOCK/BMAL1. Int J Biochem Cell Biol 2016; 78: 31-42. https://doi.org/10.1016/j.biocel.2016.06.020

Luo X, Yang X, Yang Y, Li H, Cui H, Cao X. The interrelationship between inflammatory cytokines and skeletal muscle decay from the viewpoint of circadian rhythms. Arch Physiol Biochem 2022; 128: 1559-1565.https://doi.org/10.1080/13813455.2020.1782435

Mander B A, Winer J R, Walker M P. Sleep and Human Aging. Neuron 2017; 94: 19-36. https://doi.org/10.1016/j.neuron.2017.02.004

Mao Y, Fu A, Hoffman A E, Jacobs D I, Jin M, Chen K, et al. The circadian gene CRY2 is associated with breast cancer aggressiveness possibly via epigenomic modifications. Tumour Biol 2015; 36: 3533-3539. https://doi.org/10.1007/s13277-014-2989-3

Martinez-Nicolas A, Madrid J A, García F J, Campos M, Moreno-Casbas M T, Almaida-Pagán P F, et al. Circadian monitoring as an aging predictor. Sci Rep 2018; 8: 15027. https://doi.org/10.1038/s41598-018-33195-3

Mason I C, Qian J, Adler G K, Scheer F. Impact of circadian disruption on glucose metabolism: implications for type 2 diabetes. Diabetologia 2020; 63: 462-472. https://doi.org/10.1007/s00125-019-05059-6

Masuda K, Katsuda Y, Niwa Y, Sakurai T, Hirano A. Analy-

sis of circadian rhythm components in EEG/EMG data of aged mice. Front Neurosci 2023; 17: 1173537. https://doi.org/10.3389/fnins.2023.1173537

Mayeuf-Louchart A, Staels B, Duez H. Skeletal muscle functions around the clock. Diabetes Obes Metab 2015; 17 Suppl 1: 39-46. https://doi.org/10.1111/dom.12517

McKie G L, Medak K D, Knuth C M, Shamshoum H, Townsend L K, Peppler W T, et al. Housing temperature affects the acute and chronic metabolic adaptations to exercise in mice. J Physiol 2019; 597: 4581-4600. https://doi.org/10.1113/JP278221

Mehrzadi S, Pourhanifeh M H, Mirzaei A, Moradian F, Hosseinzadeh A. An updated review of mechanistic potentials of melatonin against cancer: pivotal roles in angiogenesis, apoptosis, autophagy, endoplasmic reticulum stress and oxidative stress. Cancer Cell Int 2021; 21: 188. https://doi.org/10.1186/s12935-021-01892-1

Meléndez-Fernández O H, Liu J A, Nelson R J. Circadian rhythms disrupted by light at night and mistimed food intake alter hormonal rhythms and metabolism. Int J Mol Sci 2023; 24. https://doi.org/10.3390/ijms24043392

Meneses-Santos D, Buonfiglio D D C, Peliciari-Garcia R A, Ramos-Lobo A M, Souza D D N, Carpinelli A R, et al. Chronic treatment with dexamethasone alters clock gene expression and melatonin synthesis in rat pineal gland at night. Nat Sci Sleep 2018; 10: 203-215. https://doi.org/10.2147/NSS.S158602

Míková H, Kuchtiak V, Svobodová I, Spišská V, Pačesová D, Balík A, et al. Circadian regulation of GluA2 mRNA processing in the rat suprachiasmatic nucleus and other brain structures. Mol Neurobiol 2021; 58: 439-449. https://doi.org/10.1007/s12035-020-02141-8

Miller B H, Takahashi J S. Central circadian control of female reproductive function. Front Endocrinol (Lausanne) 2013; 4: 195. https://doi.org/10.3389/fendo.2013.00195

Miller S, Aikawa Y, Sugiyama A, Nagai Y, Hara A, Oshima T, et al. An Isoform-selective modulator of cryptochrome 1 regulates circadian rhythms in mammals. Cell Chem Biol 2020; 27: 1192-1198.e5. https://doi.org/10.1016/j.chembiol.2020.05.008

Mohandas R, Douma L G, Scindia Y, Gumz M L. Circadian rhythms and renal pathophysiology. J Clin Invest 2022; 132. https://doi.org/10.1172/JCI148277

Mukherji A, Kobiita A, Damara M, Misra N, Meziane H, Champy M F, et al. Shifting eating to the circadian rest phase misaligns the peripheral clocks with the master SCN clock and leads to a metabolic syndrome. Proc Natl Acad Sci U S A 2015; 112: 6691-6698. https://doi.org/10.1073/pnas.1519807112

Nakamoto I, Uiji S, Okata R, Endo H, Tohyama S, Nitta R, et al. Diurnal rhythms of urine volume and electrolyte excretion in healthy young men under differing intensities of daytime light exposure. Sci Rep 2021; 11: 13097. https://doi.org/10.1038/s41598-021-92595-0

Noda M, Iwamoto I, Tabata H, Yamagata T, Ito H, Nagata K I. Role of Per3, a circadian clock gene, in embryonic development of mouse cerebral cortex. Sci Rep 2019; 9: 5874. https://doi.org/10.1038/s41598-019-42390-9

Oh D J, Hong H O, Lee B A. The effects of strenuous exercises on resting heart rate, blood pressure, and maximal oxygen uptake. J Exerc Rehabil 2016; 12: 42-46. https://doi.org/10.12965/jer.150258

Olcese J M. Melatonin and Female Reproduction: An Expanding Universe. Front Endocrinol (Lausanne) 2020; 11: 85. https://doi.org/10.3389/fendo.2020.00085

Onishi K G, Maneval A C, Cable E C, Tuohy M C, Scasny A J, Sterina E, et al. Circadian and circannual timescales interact to generate seasonal changes in immune function. Brain Behav Immun 2020; 83: 33-43. https://doi.org/10.1016/j.bbi.2019.07.024

Ono M, Ando H, Daikoku T, Fujiwara T, Mieda M, Mizumoto Y, et al. The circadian clock, nutritional signals and reproduction: a close relationship. Int J Mol Sci 2023; 24: 1545. https://doi.org/10.3390/ijms24021545

Ota S M, Kong X, Hut R, Suchecki D, Meerlo P. The impact of stress and stress hormones on endogenous clocks and circadian rhythms. Front Neuroendocrinol 2021; 63: 100931. https://doi.org/10.1016/j.yfrne.2021.100931

Pan X, Taylor M J, Cohen E, Hanna N, Mota S. Circadian clock, time-restricted feeding and reproduction. Int J Mol Sci 2020; 21. https://doi.org/10.3390/ijms21030831

Patke A, Young M W, Axelrod S. Molecular mechanisms and physiological importance of circadian rhythms. Nat Rev Mol Cell Biol 2020; 21: 67-84. https://doi.org/10.1038/s41580-019-0179-2

Pendergast J S, Branecky K L, Yang W, Ellacott K L, Niswender K D, Yamazaki S. High-fat diet acutely affects circadian organisation and eating behavior. Eur J Neurosci 2013; 37: 1350-1356. https://doi.org/10.1111/ejn.12133

Peng F, Li X, Xiao F, Zhao R, Sun Z. Circadian clock, diurnal glucose metabolic rhythm, and dawn phenomenon. Trends Neurosci 2022; 45: 471-482. https://doi.org/10.1016/j.tins.2022.03.010

Peng L, Zhang K, Chen K. Period circadian clock 3 inhibits

palmitic acid-induced oxidative stress and inflammatory factor secretion in podocytes. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2021; 46: 1177-1186.

Petković M, Henis M, Heese O, Relógio A. Chronotherapy in Glioblastoma: state of the art and future perspectives. EBioMedicine 2023; 89: 104470. https://doi.org/10.1016/j.ebiom.2023.104470

Piet R. Circadian and kisspeptin regulation of the preovulatory surge. Peptides 2023; 163: 170981. https://doi.org/10.1016/j.peptides.2023.170981

Pilorz V, Helfrich-Förster C, Oster H. The role of the circadian clock system in physiology. Pflugers Arch 2018; 470: 227-239. https://doi.org/10.1007/s00424-017-2103-y

Pizarro A, Hayer K, Lahens N F, Hogenesch J B. CircaDB: a database of mammalian circadian gene expression profiles. Nucleic Acids Res 2013; 41: 1009-1013. https://doi.org/10.1093/nar/gks1161

Qian J, Scheer F. Circadian system and glucose metabolism: implications for physiology and disease. Trends Endocrinol Metab 2016; 27: 282-293. https://doi.org/10.1016/j.tem.2016.03.005

Ramkisoensing A, Meijer J H. Synchronization of biological clock neurons by light and peripheral feedback systems promotes circadian rhythms and health. Front Neurol 2015; 6: 128. https://doi.org/10.3389/fneur.2015.00128

Ramsay S, Zagorodnyuk V. Role of circadian rhythms and melatonin in bladder function in heath and diseases. Auton Neurosci 2023; 246: 103083. https://doi.org/10.1016/j.autneu.2023.103083

Raun S H, Henriquez-Olguín C, Karavaeva I, Ali M, Møller L L V, Kot W, et al. Housing temperature influences exercise training adaptations in mice. Nat Commun 2020; 11: 1560. https://doi.org/10.1038/s41467-020-15311-y

Reddy S, Reddy V, Sharma S. Physiology, circadian rhythm. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC., 2023.

Refinetti R. Circadian rhythmicity of body temperature and metabolism. Temperature (Austin) 2020; 7: 321-362. https://doi.org/10.1080/23328940.2020.1743605

Richards J, Gumz M L. Mechanism of the circadian clock in physiology. Am J Physiol Regul Integr Comp Physiol 2013; 304: 1053-1064. https://doi.org/10.1152/ajpregu.00066.2013

Rivas G B S, Teles-de-Freitas R, Pavan M G, Lima J B P, Peixoto A A, Bruno R V. Effects of light and temperature on daily activity and clock gene expression in two mosquito disease vectors. J Biol Rhythms 2018; 33: 272-288. https://doi.org/10.1177/0748730418772175

Rondanelli M, Faliva M A, Perna S, Antoniello N. Update on the role of melatonin in the prevention of cancer tumorigenesis and in the management of cancer correlates, such as sleep-wake and mood disturbances: review and remarks. Aging Clin Exp Res 2013; 25: 499-510. https://doi.org/10.1007/s40520-013-0118-6

Ruan W, Yuan X, Eltzschig H K. Circadian rhythm as a therapeutic target. Nat Rev Drug Discov 2021; 20: 287-307. https://doi.org/10.1038/s41573-020-00109-w

Ruben M D, Wu G, Smith D F, Schmidt R E, Francey L J, Lee Y Y, et al. A database of tissue-specific rhythmically expressed human genes has potential applications in circadian medicine. Sci Transl Med 2018; 10. https://doi.org/10.1126/scitranslmed.aat8806

Ruby C L, Verbanes N M, Palmer K N, Zisk C F, Bunion D J, Marinos L N. Caffeine Delays Light-entrained Activity and Potentiates Circadian Photic Phase-resetting in Mice. J Biol Rhythms 2018; 33: 523-534. https://doi.org/10.1177/0748730418789236

Russell G M, Kalafatakis K, Lightman S L. The importance of biological oscillators for hypothalamic-pituitary-adrenal activity and tissue glucocorticoid response: coordinating stress and neurobehavioural adaptation. J Neuroendocrinol 2015; 27: 378-388. https://doi.org/10.1111/jne.12247

Sahar S, Sassone-Corsi P. Regulation of metabolism: the circadian clock dictates the time. Trends Endocrinol Metab 2012; 23: 1-8. https://doi.org/10.1016/j.tem.2011.10.005

Saidi O, Colin E, Rance M, Doré E, Pereira B, Duché P. Effect of morning versus evening exercise training on sleep, physical activity, fitness, fatigue and quality of life in overweight and obese adults. Chronobiol Int 2021; 38: 1537-1548. https://doi.org/10.1080/07420528.2021.1935988

Sargin D, Oliver D K, Lambe E K. Chronic social isolation reduces 5-HT neuronal activity via upregulated SK3 calcium-activated potassium channels. Elife 2016; 5. https://doi.org/10.7554/eLife.21416

Scheer F, Hilton M F, Evoniuk H L, Shiels S A, Malhotra A, Sugarbaker R, et al. The endogenous circadian system worsens asthma at night independent of sleep and other daily behavioral or environmental cycles. Proc Natl Acad Sci U S A 2021; 118. https://doi.org/10.1073/pnas.2018486118

Schibler U, Gotic I, Saini C, Gos P, Curie T, Emmenegger Y, et al. Clock-talk: interactions between central and peripheral circadian oscillators in mammals. Cold Spring Harb Symp Quant Biol 2015; 80: 223-232. https://doi.org/10.1101/sqb.2015.80.027490

Sciarra F, Franceschini E, Campolo F, Gianfrilli D, Pallotti F, Paoli D, et al. Disruption of circadian rhythms: a crucial factor in the etiology of infertility. Int J Mol Sci 2020; 21. https://doi.org/10.3390/ijms21113943

Scott M R, McClung C A. Circadian rhythms in mood disorders. Adv Exp Med Biol 2021; 1344: 153-168. https://doi.org/10.1007/978-3-030-81147-1_9

Sebti Y, Hebras A, Pourcet B, Staels B, Duez H. The circadian clock and obesity. Handb Exp Pharmacol 2022; 274: 29-56. https://doi.org/10.1007/164_2021_579

Segers A, Depoortere I. Circadian clocks in the digestive system. Nat Rev Gastroenterol Hepatol 2021; 18: 239-251. https://doi.org/10.1038/s41575-020-00401-5

Sellami M, Bragazzi N L, Slimani M, Hayes L, Jabbour G, De Giorgio A, et al. The effect of exercise on glucoregulatory hormones: a countermeasure to human aging: insights from a comprehensive review of the literature. Int J Environ Res Public Health 2019; 16. https://doi.org/10.3390/ijerph16101709

Shafi A A, McNair C M, McCann J J, Alshalalfa M, Shostak A, Severson T M, et al. The circadian cryptochrome, CRY1, is a pro-tumorigenic factor that rhythmically modulates DNA repair. Nat Commun 2021; 12: 401. https://doi.org/10.1038/s41467-020-20513-5

Sherman H, Gutman R, Chapnik N, Meylan J, le Coutre J, Froy O. Caffeine alters circadian rhythms and expression of disease and metabolic markers. Int J Biochem Cell Biol 2011; 43: 829-838. https://doi.org/10.1016/j.biocel.2011.02.008

Shuboni-Mulligan D D, Young D L, Jr., De La Cruz Minyety J, Vera E, Munasinghe J, Gall A J, et al. Impact of age on the circadian visual system and the sleep-wake cycle in mus musculus. NPJ Aging Mech Dis 2021; 7: 10. https://doi.org/10.1038/s41514-021-00063-w

Silva C C, Domínguez R. Clock control of mammalian reproductive cycles: Looking beyond the pre-ovulatory surge of gonadotropins. Rev Endocr Metab Disord 2020; 21: 149-163. https://doi.org/10.1007/s11154-019-09525-9

Singh R, Singh R K, Masood T, Tripathi A K, Mahdi A A, Singh R K, et al. Circadian time structure of circulating plasma lipid peroxides, antioxidant enzymes and other small molecules in peptic ulcers. Clin Chim Acta 2015; 451: 222-226. https://doi.org/10.1016/j.cca.2015.09.033

Small L, Altıntaş A, Laker R C, Ehrlich A, Pattamaprapanont P, Villarroel J, et al. Contraction influences Per2 gene expression in skeletal muscle through a calcium-dependent pathway. J Physiol 2020; 598: 5739-5752. https://doi.org/10.1113/JP280428

Sokolowska E, Viitanen R, Misiewicz Z, Mennesson M, Saarnio S, Kulesskaya N, et al. The circadian gene Cryptochrome 2 influences stress-induced brain activity and depressive-like behavior in mice. Genes Brain Behav 2021; 20: e12708. https://doi.org/10.1111/gbb.12708

Solocinski K, Gumz M L. The circadian clock in the regulation of renal rhythms. J Biol Rhythms 2015; 30: 470-486. https://doi.org/10.1177/0748730415610879

Son G H, Chung S, Kim K. The adrenal peripheral clock: glucocorticoid and the circadian timing system. Front Neuroendocrinol 2011; 32: 451-465. https://doi.org/10.1016/j.yfrne.2011.07.003

Speed J S, Hyndman K A, Roth K, Heimlich J B, Kasztan M, Fox B M, et al. High dietary sodium causes dyssynchrony of the renal molecular clock in rats. Am J Physiol Renal Physiol 2018; 314: 89-98. https://doi.org/10.1152/ajprenal.00028.2017

Stow L R, Richards J, Cheng K Y, Lynch I J, Jeffers L A, Greenlee M M, et al. The circadian protein period 1 contributes to blood pressure control and coordinately regulates renal sodium transport genes. Hypertension 2012; 59: 1151-1156. https://doi.org/10.1161/HYPERTENSIONAHA.112.190892

Tahara Y, Shibata S. Circadian rhythms of liver physiology and disease: experimental and clinical evidence. Nat Rev Gastroenterol Hepatol 2016; 13: 217-226. https://doi.org/10.1038/nrgastro.2016.8

Tahara Y, Shiraishi T, Kikuchi Y, Haraguchi A, Kuriki D, Sasaki H, et al. Entrainment of the mouse circadian clock by sub-acute physical and psychological stress. Sci Rep 2015; 5: 11417. https://doi.org/10.1038/srep11417

Takeshima M, Shimizu T, Echizenya M, Ishikawa H, Kanbayashi T. Inpatient phase-advance therapy for delayed sleep-wake phase disorder: a retrospective study. Nat Sci Sleep 2018; 10: 327-333. https://doi.org/10.2147/NSS.S179264

Talpur H S, Chandio I B, Brohi R D, Worku T, Rehman Z, Bhattarai D, et al. Research progress on the role of melatonin and its receptors in animal reproduction: A comprehensive review. Reprod Domest Anim 2018; 53: 831-849. https://doi.org/10.1111/rda.13188

Tang Q, Cheng B, Xie M, Chen Y, Zhao J, Zhou X, et al. Circadian clock gene bmal1 inhibits tumorigenesis and increases paclitaxel sensitivity in tongue squamous cell carcinoma. Cancer Res 2017; 77: 532-544. https://doi.org/10.1158/0008-5472.CAN-16-1322

Tarquini R, Mazzoccoli G. Clock Genes, Metabolism, and

Cardiovascular Risk. Heart Fail Clin 2017; 13: 645-655. https://doi.org/10.1016/j.hfc.2017.05.001

Tokuoka A, Itoh T Q, Hori S, Uryu O, Danbara Y, Nose M, et al. cryptochrome genes form an oscillatory loop independent of the per/tim loop in the circadian clockwork of the cricket Gryllus bimaculatus. Zoological Lett 2017; 3: 5. https://doi.org/10.1186/s40851-017-0066-7

Tong X, Zhang D, Charney N, Jin E, VanDommelen K, Stamper K, et al. DDB1-mediated CRY1 degradation promotes FOXO1-Driven gluconeogenesis in liver. Diabetes 2017; 66: 2571-2582. https://doi.org/10.2337/db16-1600

Tsang A H, Astiz M, Friedrichs M, Oster H. Endocrine regulation of circadian physiology. J Endocrinol 2016; 230: 1-11. https://doi.org/10.1530/JOE-16-0051

Tsang A H, Barclay J L, Oster H. Interactions between endocrine and circadian systems. J Mol Endocrinol 2014; 52: 1-16. https://doi.org/10.1530/JME-13-0118

Tse A C, Lee P H, Zhang J, Chan R C, Ho A W, Lai E W. Effects of exercise on sleep, melatonin level, and behavioral functioning in children with autism. Autism 2022; 26: 1712-1722. https://doi.org/10.1177/13623613211062952

Turek F W, Joshu C, Kohsaka A, Lin E, Ivanova G, McDearmon E, et al. Obesity and metabolic syndrome in circadian Clock mutant mice. Science 2005; 308: 1043-1045. https://doi.org/10.1126/science.1108750

Uenoyama Y, Tsukamura H. KNDy neurones and GnRH/LH pulse generation: Current understanding and future aspects. J Neuroendocrinol 2023; 35: e13285. https://doi.org/10.1111/jne.13285

Walker W H, Walton J C, DeVries A C, Nelson R J. Circadian rhythm disruption and mental health. Translational Psychiatry 2020; 10: 28. https://doi.org/10.1038/s41398-020-0694-0

Wang F, Li C, Yongluo, Chen L. The Circadian gene clock plays an important role in cell apoptosis and the DNA damage response in vitro. Technol Cancer Res Treat 2016; 15: 480-486. https://doi.org/10.1177/1533034615585433

Wang J, Hou W T, Qin X M, Du G H, Gao X X. [Research progress of circadian rhythm]. Zhongguo Zhong Yao Za Zhi 2021; 46: 3240-3248.

Wang M, Jing Y, Hu L, Gao J, Ding L, Zhang J. Recent advances on the circadian gene PER2 and metabolic rhythm of lactation of mammary gland. Anim Nutr 2015a; 1: 257-261. https://doi.org/10.1016/j.aninu.2015.11.008

Wang Y, Xing T, Huang L, Song G, Sun X, Zhong L, et al. Period 1 and estrogen receptor-beta are downregulated in Chinese colon cancers. Int J Clin Exp Pathol 2015b; 8: 8178-8188.

Webb J. ECT-resistant bipolar depression treated with a single course of triple chronotherapy. Case Rep Psychiatry 2022; 2022: 9957190. https://doi.org/10.1155/2022/9957190

Xie Y, Tang Q, Chen G, Xie M, Yu S, Zhao J, et al. New insights into the circadian rhythm and its related diseases. Front Physiol 2019; 10: 682. https://doi.org/10.3389/fphys.2019.00682

Yang J, Zhang Z, Zhang Y, Zheng X, Lu Y, Tao D, et al. Clock interacts with RANBP9 and is involved in alternative splicing in spermatogenesis. Gene 2018; 642: 199-204. https://doi.org/10.1016/j.gene.2017.11.007

Ye L, Wu H, Xu W. Deletion of Bmal1 impairs pancreatic β-cell function via mitochondrial signaling pathway. Biomed Res Int 2020; 2020: 9803024. https://doi.org/10.1155/2020/9803024

Youn S, Choi B, Lee S, Kim C, Chung S. Time to Take Sleeping Pills and Subjective Satisfaction among Cancer Patients. Psychiatry Investig 2020; 17: 249-255. https://doi.org/10.30773/pi.2019.0216

Yu F, Liu Y, Zhang R, Zhu L, Zhang T, Shi Y. Recent advances in circadian-regulated pharmacokinetics and its implications for chronotherapy. Biochem Pharmacol 2022; 203: 115185. https://doi.org/10.1016/j.bcp.2022.115185

Yun S, Lee E J, Choe H K, Son G H, Kim K, Chung S. Programming effects of maternal stress on the circadian system of adult offspring. Exp Mol Med 2020; 52: 473-484. https://doi.org/10.1038/s12276-020-0398-9

Zhang J, Sun R, Jiang T, Yang G, Chen L. Circadian blood pressure rhythm in cardiovascular and renal health and disease. Biomolecules 2021; 11. https://doi.org/10.3390/biom11060868

Zhang S, Dai M, Wang X, Jiang S-H, Hu L-P, Zhang X-L, et al. Signalling entrains the peripheral circadian clock. Cellular Signalling 2020; 69: 109433. https://doi.org/10.1016/j.cellsig.2019.109433

Zhang W X, Chen S Y, Liu C. Regulation of reproduction by the circadian rhythms. Sheng Li Xue Bao 2016; 68: 799-808.

Zhang Y, Meng N, Bao H, Jiang Y, Yang N, Wu K, et al. Circadian gene PER1 senses progesterone signal during human endometrial decidualization. J Endocrinol 2019. https://doi.org/10.1530/JOE-19-0284

Zheng D, Ratiner K, Elinav E. Circadian influences of diet on the microbiome and immunity. Trends Immunol 2020; 41: 512-530. https://doi.org/10.1016/j.it.2020.04.005

Zhou J, Wang J, Zhang X, Tang Q. New Insights into can-

cer chronotherapies. Front Pharmacol 2021; 12: 741295. https://doi.org/10.3389/fphar.2021.741295

Zhou X, Yu R, Long Y, Zhao J, Yu S, Tang Q, et al. BMAL1 deficiency promotes skeletal mandibular hypoplasia via OPG downregulation. Cell Prolif 2018; 51: e12470. https://doi.org/10.1111/cpr.12470

Zietara A, Spires D R, Juffre A, Costello H M, Crislip G R, Douma L G, et al. Knockout of the circadian clock protein PER1 (Period1) exacerbates hypertension and increases kidney injury in dahl salt-sensitive rats. Hypertension 2022; 79: 2519-2529. https://doi.org/10.1161/HYPERTENSIONAHA.122.19316

Zuber A M, Centeno G, Pradervand S, Nikolaeva S, Maquelin L, Cardinaux L, et al. Molecular clock is involved in predictive circadian adjustment of renal function. Proc Natl Acad Sci U S A 2009; 106: 16523-16528. https://doi.org/10.1073/pnas.0904890106