Stress and Circadian Rhythms

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Abstract

Our lives are dominated by circadian rhythms (which last about a whole day), most notably through the sleep-wake cycle. Almost all important physiological and metabolic processes are controlled by circadian rhythms. The ability to predict day-night changes in the environment gives most species on earth an evolutionary advantage. As a result, from plants to higher mammals, organisms form endogenous biological clocks in order to adapt to circadian rhythm changes. In the absence of external time indicators, the internal clock can automatically run on a cycle of about 24 h. Stress responses begin with a local physical (such as skeletal muscle contusion) or mental (such as loss of a loved one) stressor but always end up with a broad, systematic process of response that affects many organs and systems. It is normal, then, that disorders of circadian rhythm put the body in a state of stress that leads to various mental, neurological, and metabolic disorders.

Keywords

Circadian rhythm · Stress · Molecular clock · HPA axis

Plants to higher mammals on earth have adapted to the 24 h cycle by the evolution of internal rhythms, named circadian clocks, which adjusts physiology and behavior to

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the repeating changes in around environmental conditions. In mammals, the main pacemaker in the suprachiasmatic nucleus (SCN) of the hypothalamus receives ambient light changes in order to synchronize peripheral tissue and central non-SCN clocks with circadian rhythm changes. Regulatory systems, such as the autonomic nervous system (ANS) and the thalamic-pituitary-adrenal (HPA) axis, are most important in modifying stress responses that receive strong circadian input.

8.1 Stress

Stress, which was proposed by Hans Selye about 80 years ago, is a physiological response of the body to changes in the environment and is now a basic scientific, social, and clinical concept [1, 2]. Stress response is the typical response of attention, such as arousal and emotion, emphasizing the stress, awakening, and emotional change caused by environmental stimulus stressor. Stressors include psychogenic (e.g., social stimuli) or neurogenic (e.g., painful stimuli) or a combination of both; this issue comprises results to which connect with psychogenic stressors. Stressors can affect mammals in the womb. Postnatally, environmental stressors can affect external stress that can be transmitted from a lactating mother to her offspring.

Some studies focus on the intrinsic factors that form individual stress response. It suggests that any stressor is heterogeneous, depending on internal factors such as gender, genes, and age. This was confirmed in a retrospective study of rodents. Some researches show to the fore the essential role of the circadian clock in intermediate between the individual's stress response and the environmental stressor. The main pacemaker located in the suprachiasmatic nucleus of the hypothalamus affects not only the HPA axis but also the autonomic nervous system, making both stress response systems receive strong circadian input. Therefore, the interaction between circadian rhythm and environmental stress is universal and has pathological and physiological effects.

8.2 Circadian Rhythms

Circadian rhythm is regulated by the circadian clock inside the body, which enables the body to maintain a circadian rhythm 24 h a day, and the complexity of its structure varies according to the corresponding organism [3]. The mammalian physiological system consists mainly of a central pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus, also known as the central clock, which activates ganglion cells by the eye to provide melanin to regulate the light/dark changes of the day. These light/darkness cycles are the principal external stimulus to the SCN; however, there are other periodic synchronizers, such as the schedule of ingestion/fasting and the exercise (activity/rest). SCN is the main external stimulation light/dark cycle but also other periodic synchronizers, this exercise, for example (the activity/rest), and the schedule of ingestion/fasting. These synchronize with the central pacemaker by affecting other clocks in the

body's tissues and organs, such as the heart, fatty tissues, pancreas, and lungs, through autonomic system activity and periodic hormone secretion [4]. Some molecular researches have demonstrated oscillations in the transcription of clock-specific genes that play a key part in the generation of the circadian rhythms. Many of these clock genes work as transcriptional agents that stimulated or disable their own expression in a series of feedback reactions [4].

8.3 Interaction Between Stress and Circadian Rhythms

Disruption of circadian rhythm is closely related to stressors. Repeated or long-term exposure to stressors may contribute to the development of mental illness or metabolism in rodents and humans and can result to long-lasting adaptations, such as energy metabolism [5, 6]. Stressors are vital to the characteristics of the stress response. The main stressors were social interaction, environmental factors, constant light exposure, hot and cold stimulation, and increased shift work. It is important to realize that these changes not only affect the activity of the hypothalamus but may also lead to the development of a range of stress-related diseases Light is of the most important direct causes of circadian dysrhythmias. In rodent animals after 60 min short pulse of light exposure can be found to increase plasma corticosterone. This rise has both been characterized as ACTH-independent in rodents. However, there was ACTH-dependent contribution by the HPA axis in mice [7]. However, light is not the only cause of high corticosterone. The day cycle is shortened by 1 h (9.5 h light vs. 13.5 h dark), and the GCs in the cycle are not aligned with the adrenal ACTH but with behavior and the SCN clock [8]. Similarly, the effect of food on circadian rhythm cannot be ignored. Restricting mice's food intake during the day promoted GC levels to reach a second peak. Chronic circadian disruption owing to frequent and inappropriate food or light intake can effectively alter diurnal levels of secreted GCs and pressure-induced GC reactions. When suffering for a long time in stressors and disruption of circadian rhythm can result in similar pathological outcomes, such as impaired immune response, metabolic disorders [9], accelerated growth and increased death rate [10], and accelerated aging [11].

The effectors of the stress system also impact the adjustment of circadian rhythm. How does the stress system affect circadian rhythm? GCs and epinephrine are major stress effectors that act as synchronizers of the body clock and act through specific receptors. In the case of GCs, it acts as both a major stress signal and a major circadian signal throughout the body [12, 13]. Two kinds of mammalian intracelluar receptors for CORT have been characterized and isolated – the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR), which also binds aldosterone with high affinity [14, 15] – mainly GR, because even at the lowest point of GC's circadian rhythm, MR is constrained by GCs, which makes MR signals inefficient in transmitting time information. GR is expressed in almost all organs and tissues [16–18] except SCN, where no GR expression has been detected [19]. Therefore, SCN is not controlled by direct feedback synchronization of GCs. SCN is periodic information that perceives light as darkness. But even in the absence

of light information, it can independently produce an internal circadian rhythm [20]. The increase in CORT is both a signal of stress in tissues and an entrapment signal of circadian rhythm throughout the body. Some studies believe that stress is an exaggerated arousal state, and the temporal correlation of the determinants of stress-induced CORT activity is not the temporal correlation between stress-induced CORT and the basic circadian phase of CORT. Appropriate stress response depends on the circadian rhythm changes, and this association is the initial factor in the quantitative and qualitative reaction of the cell system to stress-induced CORT secretion [21]. Many rodent studies have investigated the effects of stress on the circadian rhythm. Using the behavior failure paradigm, Tahara et al. [22] reported that stress at the start of photology leads an early phase shift in mRNA expression rhythm of several core clock genes in peripheral organs of rats. When the rats were stressed at other times of the day, the effect was phase delay and even loss of synchronicity, indicating that the effect of stress on the peripheral clock was time dependent. After a few weeks of long-term exposure to stressors, these effects are more subtle or less noticeable, suggesting habituation effects. In a longer-term approach, the effects of repeated social failures over 19 days were analyzed, both in the early dark and the early light. The amplitude of Per2 oscillations in SCN increased, while the expressions of Cry1 and Per2 were downregulated in adrenal gland under predark pressure. Conversely, stress in early light does not affect the SCN clock but causes the phase of the adrenal oscillator to advance. Phase changes in the adrenal clock were similar to those in Tahara et al. ‘s study.

8.3.1 Molecular Clock in Stress and Circadian Rhythms

The Earth rotate its axis 24 h a day; as a result, organisms on Earth have the ability to use molecular clocks to predict changes in the environment, and this has passed on the dominant genes for most species’ evolution. As a result, all living things, whether mammals or plants, have evolved an internal clock, a circadian rhythm, that allows these clocks to run almost 24 h a day without cues from external time. The internal body clock allows the body to accurately estimate the time of day, in order to align internal biological functions with environmental changes. The biological clock combines with external zeitgebers, such as light and temperature, of which light is the most favorable. The circadian clock is temperature-compensated, a feature that is particularly important for poikilotherms [23]. In 2017, Michael W. Young, Jeffrey C. Hall, and Michael Rosbash were awarded the Nobel Prize in Physiology or Medicine due to their discovery of what was the molecular machinery underpinning the biological clock 1–4 (Box 1). The molecular clocks are important to elucidate the mechanism of circadian rhythms in disease and physiology. In mammals, circadian clocks control circadian rhythmicity. These clocks, which consist of about 20,000 neurons in the suprachiasmatic nucleus of the hypothalamus, can be divided into central or peripheral clocks [24], and the peripheral clock can exist in almost any organization [25]. Light signal is received and transmitted to the master clock

through the retina and is input to the peripheral clock of the whole body by the master clock through a variety of neurohumoral signals [26].

In mammals, the biological clock is associated with a molecular oscillator in every cell in the body. The molecular oscillator is built on self-sustaining oscillations generated by transcription-translation feedback loops (TTFLs). The clock's core TTFL is consist of the muscle ant-like 1 (Bamal 1) and genes brian, cryptochrome (Cry) 1/2, period (Per)1–3, and circadian locomotor output cycles kaput (Clock) [27, 28]. In mammals of the TTFLs involves transcriptional activation by Clock/Bmal1 heterodimers, which drive 24 h expression of Cry and Per genes by E-box regulatory sequences. The suprachiasmatic nucleus (SCN) of the hypothalamus is the body's main biological clock and the fulcrum of the gene-to-cell circuit. The SCN determines the body's physiological cycle and daily rhythm of life [29].

There are innumerable cellular clocks across the organisms [30, 31], but the principal circadian pacemaker in mammals is the SCN of the hypothalamus [32]. Its highly coordinated multicellular oscillations can continue indefinitely to lead to internal synchronization of the body's cellular clocks [33]. Cry genes including Cry1 and Cry2 play a negative part of limb in the clock feedback loop. However, Per proteins have subtle effect on their cellular location Per and cry proteins accumulate in the cytoplasm and form complexes that translocate back into the nucleus where they are able to inhibit BMAL 1/CLOCK.-mediated transcription [34]. The time-keeping of cellular molecular clock in other organizations and the SCN pivots around self-sustaining TTFLs [35] in which, starting at the brain and muscle ARNT-like 1 (BMAL1; also known as ARNTL), circadian dawn (i.e., circadian time (CT) 0), heterodimers of circadian locomotor output cycles protein kaput (CLOCK), the positive regulators of the loop, drives the expression of the CRY and PER proteins, the negative regulators, via enhancer box (E- box) regulatory sequences [29]. By the end of the circadian day, the BMAL1/CLOCK heterodimer has been reactivated to start a new cycle. The cycle is stabilized by accessory loops in which BMAL1 and CLOCK drive E-box-mediated circadian expression of the nuclear receptors RORα, REV-ERBα, and REV-ERBβ, which in turn act via REV response element (RRE) sequences to suppress and activate BMAL1 transcription, respectively. Thus, the core TTFL of circadian expression of REV-ERB proteins is an output and also an input.

Besides, a novel mechanism that TFE3 and TFEB directly bind to the promoter of Nr1d1, a negative regulator of metabolism (e.g., Srebf1/Srebp1, Fasn), autophagy (e.g., Atg5, Ulk1) and several clock (e.g., Arntl/Bmal1, Npas2) genes binding to autophagy and nutrient availability with the cell-autonomous circadian clock through the regulation of gene expression [36, 37]. An additional loop regulates BMAL1–CLOCK activity by the transcriptional regulation of Bmal1. The core of hormone receptors REV-ERBβ (also known as Nr1d2) and retinoic acid-related orphan response (ROR) α, β, and γ and REV-ERBα (also known asNr1d1) include E-box elements in their promoter sequences and are under transcriptional control by CLOCK–BMAL1 [38, 39]. In fact, RORs are positive regulators of Bmal1 transcription and compare with REV-ERBs for retinoid orphan receptor response element

(RORE) connecting sites within the Bmal1 promoter; in contrast, REV-ERB proteins exert a negative feedback, banning Bmal1 transcription [40].

An important discovery in circadian rhythms is that SCN is not the only biological clock in the body. In fact, most cells and tissues, including other peripheral organs except SCN and brain regions, have circadian oscillations. Moreover, these oscillators can operate independently of the SCN [41, 42]. For example, in mammalian livers, these rhythms are regulated by the core circadian clock of TTFLs and fasting. The circadian rhythm occurring in the liver is regulated in two ways; one by the said autonomic diurnal oscillation combination of swing, on the other hand, can be affected by feeding or eating both at different times during the feeding and fasting cycle. mRNA can be produced and the transcription results have circadian rhythm and the expressed circadian rhythm is different in the periodic phase that shifts forward or backward [43].

8.3.2 HPA Axis in Stress and Circadian Rhythms

In addition to the core body temperature cycle, the circadian clock is synchronized with the environment on a 24 h cycle, and the adrenal gland plays a major role in coordinating the molecular oscillations of all biological clocks [44]. The stress system was regulated by the circadian system to make animals regulate cyclic challenges they encounter during day and night. The primary roles of the stress system are the hypothalamus–pituitary–adrenal (HPA) axis and the sympathetic nervous system. HPA axis mediates the adrenals to release glucocorticoids (GCs) when they are exposed to stress [44]. Stress is an internal or external challenge that needs the body to respond adequately to discomfort in less severe situations or to avoid pain or to survive. When the body is stressed, a complex response system is activated. It involves delayed response via HPA axis-mediated release of GCs and immediate response via activation of the autonomic nervous system (ANS) [45]. The adrenal gland among all peripheral oscillators is important to play a special part since the adrenal circadian clock can regularize release of hormones with clock-modulating properties to influence rhythms in other tissues. GCs from the intermediate zona fasciculata of adrenal gland. It is all known that corticosterone and cortisol are the main GCs in rodents and humans, respectively [46]. When organisms exposure to short- or long-term stress, it can rapidly activate the HPA axis to secret GCs. Glucocorticoid circadian rhythms are also closely related to the levels of arousal; the time of awakening of the rapid increase in glucocorticoid levels is thought to promote cognitive activity together with the activation of peripheral metabolic pathways in the muscle, liver, and adipose tissue, while at the end of the day, glucocorticoid levels fall, which helps you fall asleep [13]. Studies have shown that glucocorticoids can affect PER gene in peripheral tissues but are insensitive to the direct effect of glucocorticoids on rhythmic expression in SCN [47].

Hypothalamic paraventricular nucleus (PVH) stimulates the anterior pituitary to release corticotrophin under stress, thus promoting the synthesis and release of adrenal hormone [45, 48]. Glucocorticoids, such as corticosterone (CORT), not

only affect the brain through cellular signaling systems but also act on cellular stress by controlling gene expression [49, 50]. Furthermore, GCs improve the vigilance of the brain and prevent inflammatory processes in the body. Besides, GCs act by altering the activity of various kinases, such as mitogen-activated protein kinase, phosphoinositide 3-kinases (PI3K), and RAC-alpha serine/threonine kinase (AKT) [51, 52]; however, it is still not sure if between rhythmic HPA axis activity and circadian rhythm of GC secretion is relative. On one hand, adrenal rhythms persist after hypophysectomy, when no ACTH is present [53]; on the other hand, ACTH is able to phase-dependently reset GC rhythms [54]. Deliberately disturbing the adrenal clock can eliminate the circadian pattern of GC secretion, suggesting that the peripheral tissue clock ultimately dominates the GC secretion pattern [55]. Therefore, GC rhythmic and regular secretion plays an important role in time regulation. Given these different mechanisms of action, glucocorticoids can rapidly affect neural circuits during stress exposure and have long-term effects in the form of structural or functional plasticity. These various changes in neurological function can significantly affect the body's response to stress on a behavioral level [56, 57].

Information about stress can be gathered by all the sensory systems in the body (such as changes in blood composition, decreased blood volume, or encounters with predators) and pass it on to the brain stem [45]. Subsequent activation of the ANS and HPA axes was regulated. In terms of the HPA axis, stress-mediated activation triggers the production and release of adrenal GCs. Stress signals in amygdala, hippocampus, and prefrontal cortex are transmitted to the para-ventral nucleus (PVN), which stimulates CRH secretion and activates the HPA axis. The GCs need to be resynthesized after each trigger, resulting in a delay in the final effect response. Thus, this dynamic process is slower than (within minutes) the activation of ANS, which occurs within a few seconds of the beginning of the stress. Sympathetic preganglionic neurons in the spinal cord can be activated by stressors, leading to an increase in catecholamine secretion [58, 59]. Signals are transmitted to postganglia neurons and projected into peripheral effector organs, translating into the classic "fight or flight," or the preganglionic nerve, such as the visceral peripheral effector. Catecholamines are released through a shortcut between the visceral nerve and the adrenal medulla. When the organism receives the stressor, the HPA axis inhibits or stimulates transcription through GCs binding to the cell kernel receptor (GR) as shown in Fig. 8.1.

GCs bind to intracellular nuclear receptors (GR) to activate or repress transcription. GCs diffuse through the cell membrane and bind to cytoplasmic receptors (GR). This binding mediates dissociation of GR from heat shock proteins (hsp) and dimerization of GR molecules bound to GC. GR/GC complexes translocate into the nucleus where they bind to (negative) glucocorticoid response promoter elements ((n)GRE) and activate transcription, or they bind to nGRE, leading to transrepression. Alternatively, they affiliate with other transcription factors (TF) and regulate their action on corresponding responsive DNA elements (RE).

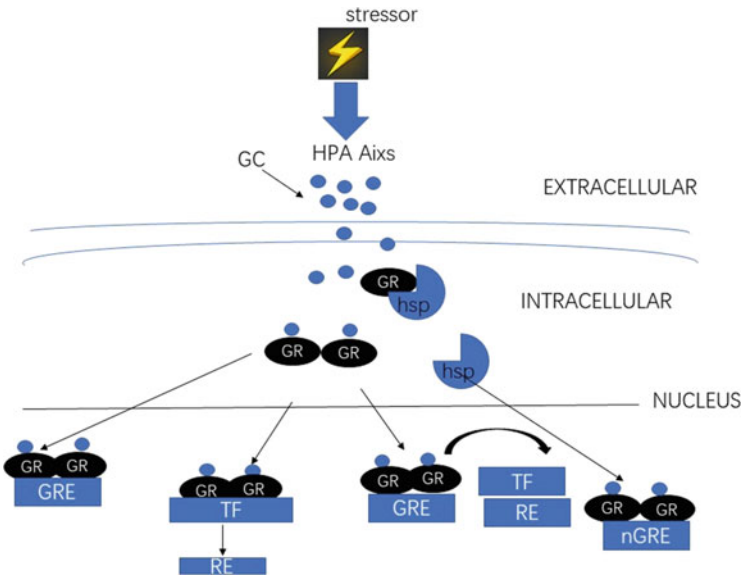

Fig. 8.1 Stress-mediated activation of the HPA axis triggers the production and release of adrenal GCs

8.4 Diseases Related to Circadian Rhythm under Stress

The term stress was first coined by Selye to explain the body's nonspecific response to any physical or psychological event that results from the transfer of physiological states within the body. He believes that stress should be divided into benign stress and malignant stress. Benign stress can positively regulate the body's function, while malignant stress will lead to the body's dysfunction and lead to disease [60]. Thus, an appropriate stress response to a variety of serious external threats is undoubtedly critical to the survival of the host [61]. The concepts of allostatic and allostatic load also enable a more detailed understanding of the mechanisms that determine an individual's susceptibility and adaptability to different physiological stresses [62, 63]. Researches have revealed that stress recovery involves a coordinated system of interactions between peripheral (body) and central (brain) signaling mechanisms [64]. Studies in rodent models and humans have clarified that SNS and the HPA axis play an important role in stress adaptation and that their dynamics also affect host flexibility to new challenges [65, 66]. Maintaining a proper time relationship between the organisms' various physiological signaling systems leads to optimal allocation of energy resources and anticipates predictable (daily) changes in the environment, thereby promoting homeostasis [67]. Thus, circadian rhythm desynchrony is related to the pathological regulation of various physiological signaling systems and is representative of the accumulation of allostatic load. This 24 h periodic rhythm is controlled by a layered circadian rhythm system, in which a

master pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus synchronizes physiological and behavioral rhythms by regulating the rhythmic activity of various neuronal and humoral allostatic mediators [41, 68]. Metabolic hormone – such as ghrelin, secreted by the stomach, and leptin secreted by adipose tissue, as an afferent signal – participates in the hypothalamus and other brain centers, thus regulating the physiological process of regulating energy homeostasis [69–71].

According to past studies, there is a clear bidirectional link between the HPA axis of stress response and the biological clock mechanism [47]. Circadian rhythms directly influence the systemic regulation of cardiovascular functions [72] and metabolic, hormonal [41], immune pathways [73]. The main effect of circadian rhythm is that chronic disruption of homeostasis increases susceptibility to systemic inflammation and metabolic disorders [73, 74]. There is a growing awareness of the negative health effects of modern lifestyles, including sleep deprivation, the mismatch between the light/dark cycle and the body clock during air travel and shift work, and also increased exposure to light at night [75]. Animal experiments have shown that chronic circadian rhythm disorders are associated with pathological disorders of many important physiological signaling systems, including neural, metabolic, and immune pathways, and behavioral changes [76–78]. Chronic circadian dysregulation in these animals results in obesity, weight gain, and disruption of metabolic hormones. In addition, the dysregulation of circadian rhythm greatly changes the response of cytokines to immune stress [79–81]. The HPA axis is necessary for maintaining circadian rhythm homeostasis not only in response to stress but also for appropriate physiological regulation of target tissues sensitive to systemic glucocorticoids [13, 44, 82].

Next, this chapter will focus on circadian rhythm-related diseases under stress, as shown in the Fig. 8.2.

The circadian rhythm cycle is the main external synchronizer of the central circadian pacemaker, but other external stimuli can affect the phase and amplitude of peripheral oscillators. The molecular mechanism generating a self-sustained circadian oscillation in SCN neurons is a complex transcriptional-translational feedback loop comprising core transcriptional activators BMAL1/CLOCK and two sets of repressors PER and CRY. The core transcriptional activators BMAL1/CLOCK regulate numerous genes. The master clock in the SCN serves to synchronize central and peripheral oscillators to optimize the function of the organism relative to the 24 h periodicities in the environment. Signals from peripheral tissues can affect the phase and amplitude of the central pacemaker.

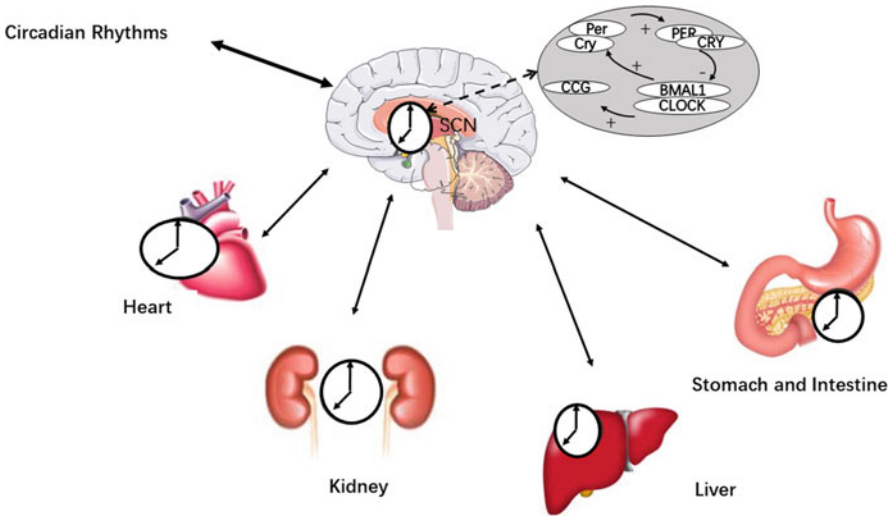

Fig. 8.2 Relationship between circadian rhythm and disease

8.4.1 Cardiovascular Disease in Circadian Rhythms and the Molecular Clock

Circadian rhythm is an important regulator of cardiovascular physiology and diseases. Each type of cardiovascular cell has a peripheral clock [83–86] that regulates various physiological functions, such as heart rate, blood pressure and endothelial function [87, 88], as well as acute myocardial infarction and the onset of arrhythmia. Almost all cell types have a functional circadian clock [25]. Core elements of the clock, such as CLOCK and BMAL1 – CLOCK and BMAL1 proteins form a complex heterodimer – function not only to connect to the E-boxes but also to sustain the clock turning of clock-controlled genes to realize the rhythmic activation of the various parts of the genome, consequently leading to a negative feedback loop with a period of approximately 24 h in bodily functions [82]. The expression levels of core clock genes in human embryonic stem cells, including BMAL1 and PER2, gradually increased during cardiac differentiation [89, 90]. The molecular clock has specific roles within each type of cardiovascular tissue, such as cardiac progenitor-like cells, endothelial cells, vascular smooth muscle cells, and fibroblasts [91]. In cardiovascular system, the circadian clock was discovered in veins and arteries, mouse aortas, vascular smooth muscle cells cultured from cultured cardio-fibroblasts, and transgenic rats [92–94]. In addition to the blood system, circadian rhythms have been exploited in myocardial stromal fibroblasts, cardiac progenitor-like cells, and cardiomyocytes [86, 95]. In the vascular system, the circadian clock is involved in thrombosis, signaling resident cells, and vascular function [96]. These observed daily fluctuations are associated not only with fluctuations in intrinsic vascular properties but also with daily sleep and wake

cycles [97, 98]. Many studies have highlighted the important physiological role of the biological clock in the cardiovascular system [99–101].

When a rodent's circadian rhythm is out of synchrony with its environment, the animal can develop myocardial fibrosis, cardiomyopathy, and systolic dysfunction, leading to cardiovascular death [102, 103]. Many studies have shown a clear relationship between various cardiovascular risk factors and circadian rhythm disorders and vice versa [104–107]. Myocardial infarction is a good example of disruption of circadian rhythm and circadian clock. Studies have shown that myocardial infarction occurs early in the morning and causes more damage and dysfunction than in the afternoon [108–111].

8.4.2 The Relationship Between Circadian Rhythm and Brain Gut Axis Diseases

Studies have shown that intestinal microbes not only affect the metabolism, digestion, and immune functions of the host but also regulate the mental state and sleep of the host through the microbial-gut-brain axis, including *Firmicutes* and *Bacteroidetes*, *Proteus*, *Actinomycete*, *Clostridium*, *Verrucomicrobia*, and *Cyanobacteria*. There are about 1000 species of microbiota in the adult gut [112]. The microbiome-visceral-brain (MGB) axis has become a hot topic of research. In this axis, the microbiomes in the intestinal tract affect brain function in three ways to generate bidirectional information flow [113–117], including immunoregulatory pathway, neuroendocrine pathway, and vagus nerve pathway. The gut nervous system connects the gut to the brain through the vagus nerve [118] and forms information transmission pathway, which can be called the gut microbe-intestinal nervous system (ENS)-vagus-brain pathway. In addition, neurotoxic metabolites such as ammonia produced and d-lactic acid by intestinal flora may enter the central nervous system through the vagus nerve, thereby affecting stress response, brain function, and circadian rhythm [119, 120]. The intestinal microbiota showed circadian rhythm in population functional and structure activity. Studies have shown that the daily variation of 60% flora, including *Clostridiales*, *Lactobacillus*, and *Bacteroidales*, leads to specific taxonomic configuration [121]. Studies have shown that sleep deprivation, circadian clock dysregulation, and shift experience alter microbial community structure and circadian clock gene expression [122–125]. Changes in sleep patterns in mice also affected the structure and diversity of intestinal microbiota [126]. Therefore, there must be a specific link between the intestinal microbiota and the host circadian clock. The body's biological clock works in concert with the microbial clock, and when the host's circadian rhythm is disrupted, it changes the balance of the intestinal microbiome, similar to changes found in human shift work [127, 128]. Studies have shown that some host clock genes such as Per1, Per2, and Bmal1 are closely related to the change of intestinal microbial rhythm [121, 129].

8.4.3 The Relationship Between Circadian Rhythm and Liver Diseases

The liver is an important metabolic center, and many of its functions must adapt to changes in circadian rhythms. As a result, the liver also has an internal clock that maintains physiological processes throughout the day. In fact, all metabolic activities in the gastrointestinal tract and liver have a biological clock. A daily rhythm is regulated by the gastrointestinal tract, liver, and food. And the process of food and clock control is interactive in many cases not easily separated. Under the action of the cell circadian oscillator, a large number of genes produce regular daily changes in physiology and behavior through rhythmic expression [130]. PER and CRY's negative feedback loop is at the heart of the mammalian molecular clock. Over time, PER and CRY accumulate in cells, eventually inhibiting transcription at their own loci. The stability of core oscillator is realized by the nuclear receptor of ROR, REV-ERBA, and REV-ERBB through regulating the expression of Bmal1. With posttranscriptional regulation of these gene products, the clock can be fine-tuned [131]. Peripheral oscillators such as the liver clock are coupled to cells and physiological mechanisms of the body through energy- and nutrient-sensing systems such as AMPK [132], PPARGC1A [133], metabolic feedback loops involving metabolites such as polyamines, and nuclear hormone receptors and nuclear hormone receptor signaling pathways [134]. Therefore, peripheral clocks are obviously affected by cell metabolism, the physiological and metabolic state of the surrounding tissue, and serum-borne signals [135]. Genome-wide expression studies have shown the importance of biological clock in the physiological activities of the liver [86, 136–138]. At the end of the light and dark phases, there are two peaks of rhythmically regulated transcripts that are respectively observed in mouse liver. Metabolic enzyme cycle and transcription are relatively constant throughout the day, indicating that the body also participates in the regulation of liver circadian rhythm after transcription. The liver metabolome indicates that the transcription of some circulating metabolic enzymes is relatively stable throughout the day, suggesting that posttranscriptional mechanisms are also involved in the diurnal regulation of liver function [139, 140].

Transcriptome analyses illustrated that the liver are rhythmically controlled in most core functions, such as metabolic pathways [136–138]. The liver may be able to maintain energy stability by regulating liver gene expression in liver cells through circadian mechanisms [141, 142]. The liver plays an important role in regulating glucose homeostasis. The biological clock seems to provide a rhythmical baseline for regular and repeated changes in glucose supply. Damage to the essential clock gene Bmal1 in mouse liver leads to excessive fluctuations in blood glucose levels, mainly in the post-absorption phase controlled by the current dominant clock in the SCN [143].

8.5 Conclusion

With the change of lifestyle, the relationship between stress and circadian rhythm has been paid more and more attention. There is a growing understanding of stress. Stress is not only a local stimulus to the body but also affects the whole body function. When the internal molecular clock of the body is out of sync with the circadian cycle of the environment, it will cause pathological changes in the body, leading to a variety of diseases such as metabolic diseases, anxiety and depression, tumors, and so on. However, the daily life of modern people can be seen everywhere because of overtime work duty, and high-intensity social, work, and life pressure, which leads to the disruption of circadian rhythm. At the same time, due to the development of the Internet era, more and more people are addicted to online games all day, many office workers are used to shopping online at night, and so on, so the internal clock is inconsistent with the external environment. Now more and more people are in a state of chronic stress, which seriously affects their work and life.

By analyzing the literature of the past decades, it is not difficult to find that the body is in a chronic state of stress due to the long-term inconsistency of circadian rhythm, from the nerve, endocrine, immune, and other aspects of body function. The most obvious one is that it affects the function of HPA axis and causes the secretion of GCs and ACTH to be out of balance, so the body is in a state of stress.

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