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Effects of environmental and social stressors on biological rhythms

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Abstract Life in contemporary society is increasingly stressful, and the body is unconsciously exposed to various stressors involving physical, biological, chemical, and social/psychological factors. Exposure to these stressors causes definite biological responses in the body, termed 'general adaptation syndrome'. Rapid endocrine responses are among the most important reactions following exposure to stressors. These include glucocorticoid and catecholamine secretion into the bloodstream, and are initial biological responses to the stressors. These responses are necessary for the 'fight-or-flight' response and must often occur rapidly for the organism to survive. Most biological events, including rapid endocrine responses, also exert effects on circadian rhythms. Indeed, disruption of biological circadian events contributes to numerous diseases, including psychological disorders, immunopathy, serious disorders of the eye, and increases in the incidence of metabolic syndrome components such as obesity, type 2 diabetes, and dyslipidemia. There is increasing evidence that exposure to stressors can affect the amplitude and/or cycle of biological circadian rhythms, and consequently aggravate and/or provoke adverse diseases. In this review, we provide an overview of the relationship between stressors and the stress response, based mainly on results from animal studies. The effects of environmental and social stressors on circadian rhythm are also discussed.

Keywords : catecholamines, circadian rhythm, general adaptation syndrome, glucocorticoids, non-specific response, stressor

Introduction

In recent decades, the phenomenon of increased stress in modern society has been widely reported, with reports suggesting a progressive increase in the incidence of diverse daily stress-related health problems, including cancer, obesity, infections, and heart disease. Therefore, it is important to understand the physiological responses in the body system under this stress exposure to reduce the potential negative effects.

The term 'stress' has been debated considerably because of a lack of a universally accepted definition. The word 'stress' was first used in the field of physical science to express distortion. In the 1930s, Hans Selye, a proponent of stress theory, published studies outlining 'stress' in the field of medical and physiological sciences[1,2]. For example, hypertrophy of the adrenal gland and atrophy of the thymus, lymph nodes, and spleen was reported after injection of ovarian extracts into rats. Similar responses were also observed after injection of extracts from the placenta, pituitary, and spleen, chemicals such as formalin and hormones, in heat and cold environments[3]. Consequently, he defined 'stress' as a 'non-specific response of the body to any demand for change'.

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Fig. 1 indicates the illustration of these definitions with some modifications. According to his stress-response theory, there are two major components of stress: (1) the 'stressor', composed physical factors (e.g., light, noise, heat, cold), biological factors (e.g., virus, pollen, bacteria), chemical factors (e.g., formalin, cigarette smoke, exhaust gas), and social/psychological factors (e.g., human relationships, shift work, distress), and (2) the 'stress response', such as hormone secretion, increased blood pressure, and blood glucose, in addition to some of the physiological responses described above. Importantly, such stress responses are not specific to particular stressors[1,4]. At present, 'stress' is defined as 'a state of homeostasis threatened by stressors that is re-established by a complex repertoire of physiologic and behavioral adaptive responses of the organism'[5].

Recent studies suggest that many biological processes display an endogenous oscillation of approximately 24 h (circadian rhythm), while disruption of biological circadian events can cause numerous diseases including psychological disorders, immunopathy, serious disorders of the eye, and components of metabolic syndrome such as obesity, type 2 diabetes, and dyslipidemia[6-10]. The biological processes underlying circadian rhythms include stress responses such as secretion of blood catecholamines and glucocorticoids, and regulation of blood

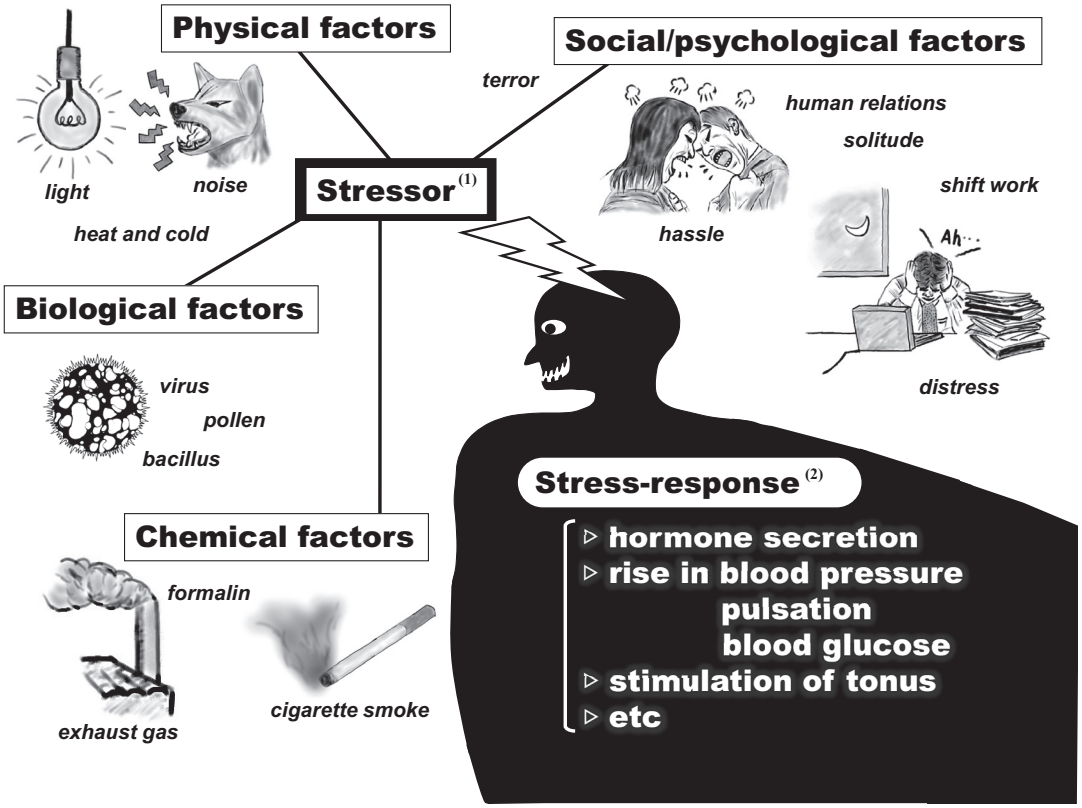

Fig. 1 Nonspecific stress-response theory. According to the stress-response theory defined by Hans Selye[4], there are two major components of stress: (1) 'stressor' composed of physical factors (e.g., light, noise, heat, cold), biological factors (e.g., virus, pollen, bacillus), chemical factors (e.g., formalin, cigarette smoke, exhaust gas), and social and psychological factors (e.g., human relationships, shift work, distress), and (2) 'stress response', including hormone secretion, rise in blood pressure, and increased blood glucose, in addition to the various physiological responses described above.

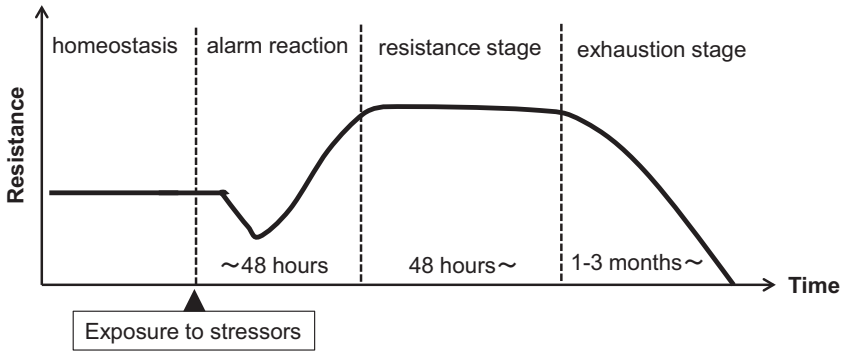

Fig. 2 General adaptation syndrome. Animals exposed to non-specific stressors show this typical syndrome, which develops in three stages. (1) alarm reaction stage: decreased thymus, spleen, lymph glands, and liver size is observed; (2) resistance stage: the adrenals are greatly enlarged but regain their lipoid granules; and (3) exhaustion stage. The animals build up resistance, where in the later part of the second stage the appearance and function of the organs returns to normal if stressor is continued at a relatively low intensity. However, with continued exposure, the animal may lose its resistance and succumb to symptoms similar to those seen in the alarm reaction.

pressure[11,12]. Thus, studying the biological changes in circadian rhythms in response to stressors is now recognized as critical for improving our understanding of biological rhythm-related illnesses.

In this review, we outline the relationships between stressors and stress responses, obtained mainly by animal studies, and discuss the effects of environmental and social stressors on circadian rhythm.

General adaptation syndrome

Selye first advocated the 'general adaptation syndrome'[13]. Briefly explained, animals exposed to severe non-specific stressors show typical responses that develop in three stages (Fig. 2). During the first stage - less than 48 h after initial stressor exposure - there is a rapid decrease in the size of the thymus, spleen, lymph glands,

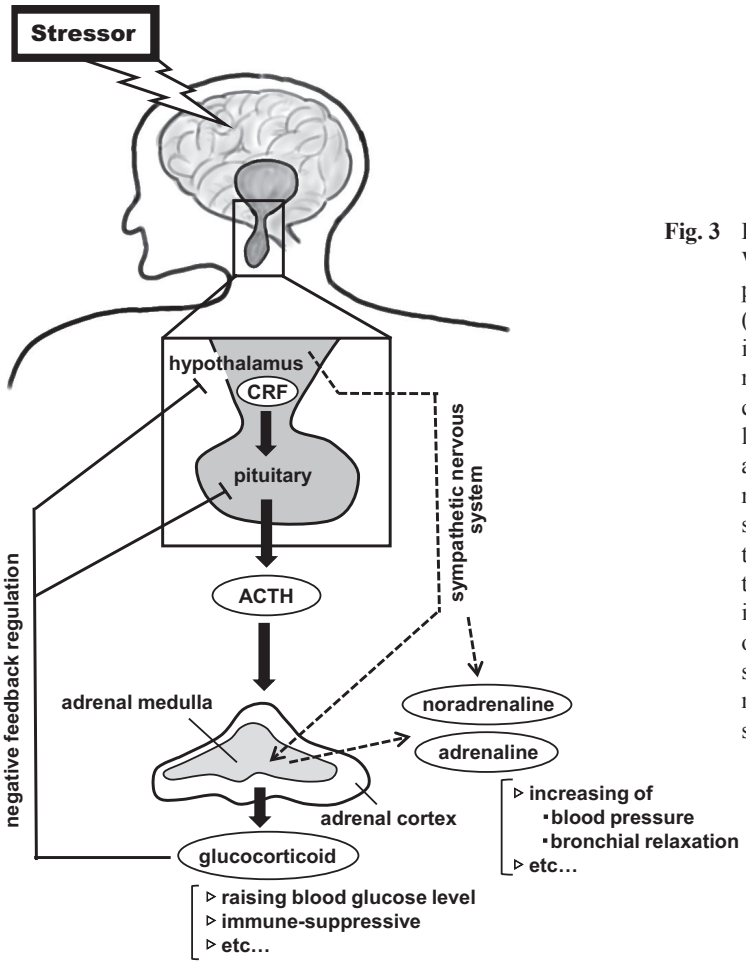

Fig. 3 Rapid endocrine response to the stressor. When vertebrate animals are exposed to the prototypical acute stressor, catecholamines (adrenaline and noradrenaline) are secreted into the bloodstream from the sympathetic nervous system (SNS). At the same time, corticotropin releasing factor (CRF) is released from the hypothalamus, and pituitary adrenocorticotropic hormone (ACTH) is immediately secreted. Glucocorticoids are then secreted within a few minutes. Eventually, the major effect of glucocorticoid release is to preserve blood glucose for the brain during stressor exposure. These alterations that occur under exposure to stressors are necessary for the 'fight-or-flight' response and must often occur rapidly for the organism to survive.

and liver (alarm reaction). In the second stage - after 48 h of exposure - the adrenals are markedly enlarged, but regain their lipoid granules (resistance stage). In the third stage, if stressor exposure is continued at a relatively low intensity, animals can build up resistance so that organ appearance and function return almost to normal. However, with continuing stressor exposure, the animal can lose resistance and exhibit symptoms similar to those seen in the alarm reaction period after 1 to 3 months of exposure (exhaustion stage).

Rapid endocrine response to stressors

During the alarm reaction period, diverse biological responses are induced following exposure to stressors. One of the most rapid reactions is endocrine response (Fig. 3). According to Sapolsky et al.[14], when vertebrate animals are exposed to a prototypical acute stressor, such as an attack by a predator, catecholamines (adrenaline and noradrenaline) are secreted into the bloodstream from the sympathetic nervous system within seconds. The sources of the circulating secreted catecholamines are generally the adrenal medulla (~80% adrenaline, ~20% noradrenaline) and the sympathetic nerves (~100% noradrenaline)[15].

Catecholamine secretion is required to induce changes in the function of the visceral organs, smooth muscles, and glands, which are required to adapt and cope with stressors[15]. At the same time, corticotropin-releasing factor (CRF) is released from the hypothalamus, followed by pituitary adrenocorticotropic hormone (ACTH) secretion[14]. Within a few minutes, the steroid hormones (glucocorticoids) are then secreted and can promote gluconeogenesis in the liver and decrease glucose uptake in the skeletal muscle and white adipose tissue[16]. Additionally, hepatic glycogen storage is increased in the liver. Eventually, the major effects of glucocorticoids are to preserve blood glucose for the brain during exposure to stressors. Glucocorticoids also exert potent immunosuppressive and anti-inflammatory effects[17], and play a role in the maintenance of blood pressure[18]. These changes following exposure to stressors are necessary for the 'fight-or-flight' response and often must occur rapidly for the organism to survive[15].

These rapid endocrine responses to stressors are widely used as biomarkers indicating acute stress responses in animal and clinical studies[19-21]. Importantly, sustained- and hyper- secretion of glucocorticoids can lead to arterial hypertension, arteriosclerotic cardiovascular disease, and psychological dysfunction[18,22]. Furthermore, epidemiological and animal studies suggest that daily exposure to stress can promote the development of breast cancer, while the processes involved in cancer progression including angiogenesis, invasion, and metastasis

are enhanced by α_2-adrenarine receptor (AR) mediated signaling[23,24]. We have also reported that noradrenalin can promote invasion of MDA-MB-231 human breast cancer cells through the α_2-AR response[25].

Clock-related genes and their oscillation

The majority of biological processes in living organisms can show typical circadian rhythms revolving around a 24 h cycle. These circadian rhythms are produced by a complex transcriptional-translational negative feedback loop[12,26,27]. As shown in Fig. 4, the transcriptional regulators, circadian locomotor output cycles kaput (CLOCK) and brain and muscle ARNT-like protein 1 (BMAL1), form a heterodimer. The CLOCK/BMAL1 heterodimer is a positive regulator, and activates expression of genes with E-box elements in the promoter regions, termed clock-controlled genes (CCGs), which encode essential regulators of hormonal and metabolic control. The proteins encoded by the major CCGs, period (PER) mRNA and cryptochrome (CRY) mRNA, make a heterodimer (PER/CRY) that can suppresses its own gene transcription by regulating CLOCK/BMAL1 heterodimer activity. This negative feedback loop acts as an oscillator *via* the alternating actions of transcription activators and repressors. Additionally, the CLOCK/BMAL1 heterodimer activates the nuclear receptor subfamily 1, group D, member 1 (REV-ERBα) and RAR-related orphans receptor α (RORα), which regulate CLOCK and BMAL1 production *via* ROR responsive elements (RORE) in their promoter regions. In rodents, various internal organs such as the brain, adrenal gland, liver, kidney, and duodenum mucosa have been found to exhibit diurnal changes in a variety of clock genes including *Clock*, *Bmal1*, *Per1* and *Cry1*[12,28-31].

Rodents are nocturnal animals, and their active and inactive phases are in the opposite phase to diurnal animals such as humans. However, the rhythmicity of the clock genes shows a similar timing of switching between active/inactive phases in both nocturnal and diurnal animals, suggesting similar control over circadian rhythms by clock gene expression[32]. As described above, this negative feedback loop revolves around a 24 h cycle, resulting in free-running circadian rhythms, indicating oscillation on a cycle slightly longer than 24 h. However, these circadian rhythms are converted to accurate 24 h diurnal rhythms by resetting the clock genes located within the suprachiasmatic nuclei (SCN), the so-called 'central clock', with light exposure in the morning[27]. Clock genes located in the peripheral organs such as the liver, kidney, and adrenal gland receive regulatory information from the central clock through neural and humoral signals, and also contribute to the rhythmic release of glucocorticoid hormones[33]. Interestingly, glucocorticoids reset and phase delay (shift) in the peripheral circadian rhythm without affecting the central clock, due to regulation of CCGs such as *Per1* and *Per2*. Importantly, in animal studies, mutations of the clock genes *Clock* and *Bmal1* were reported to cause abnormalities in sympathetic activity, vasculature, and stressor responses[34,35]. Furthermore,

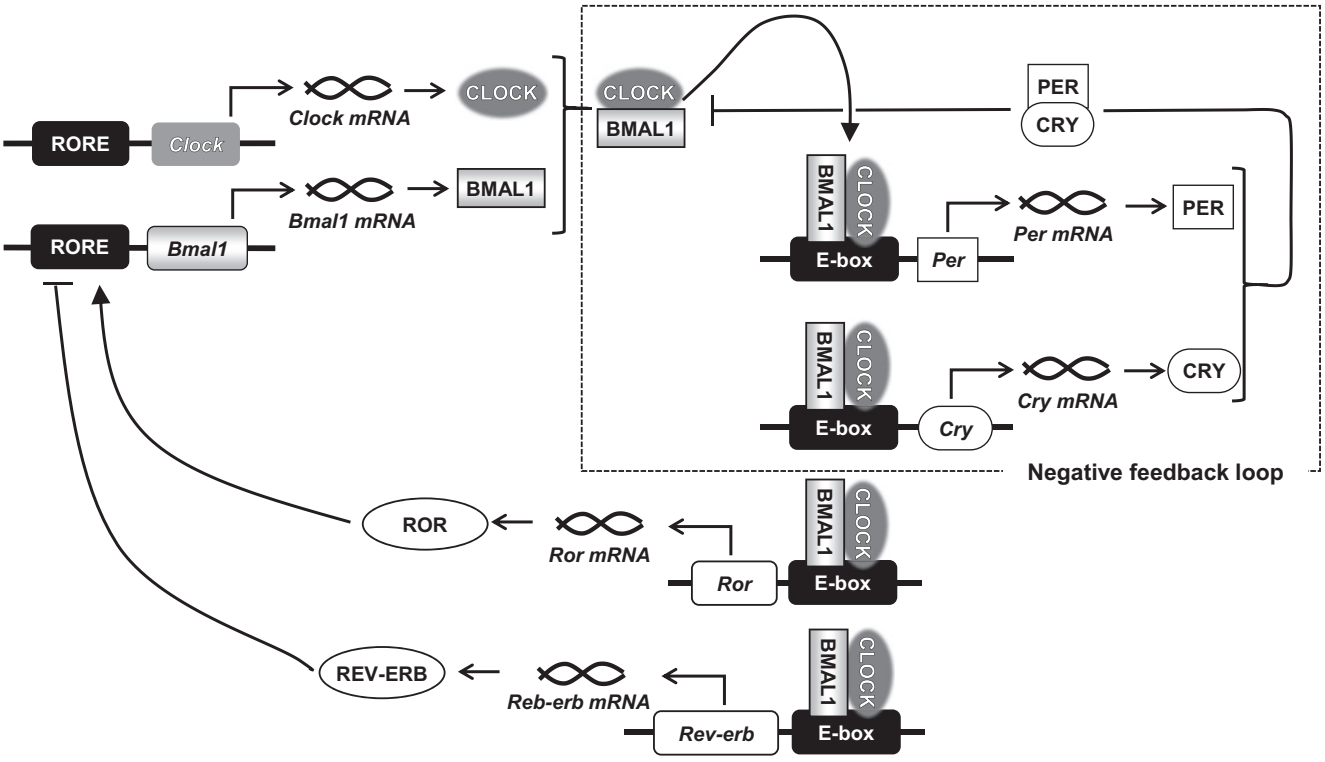

Fig. 4 The negative feedback loop mechanism responsible for circadian rhythm generation.

disruption of the clock components CLOCK and BMAL1 can result in several adverse diseases including hypoinsulinemia and diabetes[36]. Finally, clock genes also play an important role in mammalian energy balance[37]. Overall, these studies suggest that circadian disruptions of clock genes and biological events may be a cause of numerous diseases including hypertension, obesity, and diabetes.

Diurnal rhythm profiles of the rapid endocrine response to a stressor

As described, when exposed to stressors, CRF is released from the hypothalamus, followed by ACTH secretion from the pituitary gland, and glucocorticoid secretion from the adrenal cortex. In addition to part of the body's rapid stress response, ACTH and glucocorticoid secretions are widely recognized to show diurnal variations, with a nadir of plasma levels of ACTH and glucocorticoids (corticosterone for rodents and cortisol for humans) observed around the middle of the inactive (sleeping) phase, followed by a progressive increase that peaks around the time of awakening[29,38,39]. As dietary energy intake does not occur during the sleeping period, blood levels of glucose as an energy source are decreased, particularly at the time of awakening. These biological rhythms suggest that glucocorticoid secretion at awakening might prepare the organisms for the upcoming wake period and associated energy demands *via* stimulation of gluconeogenesis. As for glucocorticoids, there are also distinct circadian variations in circulating catecholamines (adrenalin and noradrenalin)[39]. Interestingly, the incidence rates of adverse cardiovascular diseases, including sudden cardiac death and myocardial infarction, show a prominent circadian variation, with a low incidence during the night and increased incidence in the morning[40-42]. Platelet aggregability, which may play a causative role in these disorders, was also reported to increase after awakening[40], suggestive of a circadian rhythm. Furthermore, the circadian rhythms of several humoral hormones, including adrenaline, noradrenaline, and glucocorticoids, may be a regulatory mechanism of circadian rhythms in circulating platelet functions[43].

Effects of physical and social/psychological stressors on biological rhythms

There is strong evidence that exposure to stressors can affect biological rhythms, especially regarding clock genes and rapid endocrine responses to a stressor. Below, we discuss the effects of common physical and social/psychological stressors on biological rhythms.

1. Nocturnal light exposure

Use of artificial lightning has increased worldwide in urban and rural areas[44], and there is increasing evidence that nocturnal exposure to artificial light can have negative impacts on health. In rodents, nocturnal light exposure suppresses concentrations of pineal melatonin and activity of N-acetyltransferase, the enzyme that synthesizes the precursor of melatonin[45-48]. Endogenous melatonin levels show an opposite phase of circadian rhythm when compared to glucocorticoids and catecholamines, with an increase in the evening approximately 2-3 h before sleep, and a peak at the middle of the sleeping period[49]. Levels of corticosterone and catecholamine are also increased with exposure to nocturnal light[50,51].

Clock gene expression is affected by nocturnal light exposure in mice, although the effect can vary depending on the time of night[52]. We previously reported that nocturnal light exposure for 1 h at the beginning of the dark period increased gene expression of hepatic *Bmal1*, *Clock*, and *Per1* in mice, indicating that the light signal is propagated to peripheral organs and can affect the amplitude and/or cycle of clock genes[53]. Additionally, nocturnal light exposure can affect the plasminogen system (PA), which plays an important role in vascular homeostasis and constitutes a critical response mechanism to cardiovascular injury, such as myocardial infarction. Plasminogen activator inhibitor-1 (PAI-1) is one of the major components of the PA system, and shows a typical circadian rhythm reaching peak levels around the time of awaking[54,55], along with increased hepatic gene expression of PAI-1. Circulating PAI-1 levels were also reported to be increased by nocturnal light exposure in mice. Overall, these findings imply that nocturnal light exposure may be a risk factor for adverse cardiovascular diseases *via* up-regulation of the PA system in the morning. Additionally, it was reported that secretion of adrenalin and noradrenalin was significantly increased at 1 h after light exposure, while corticosterone was markedly increased at 3 h after exposure, suggesting that these may be typical non-specific responses to the stressors.

2. Restraint stressor

The restraint model is commonly used to investigate the stress response in terms of physiological phenomena *in vivo*, and restraint is a preferred means of stressing animals, largely because it is straightforward and painless and without lasting debilitation[56]. A number of variations in effecting restraint have been published, and common to all methods of restraint is the restriction and immobilization of movement[57]. Induction of restraint in rats induced an increase in plasma corticosterone with HPA axis activation[58,59], as well as upregulation of pineal or plasma melatonin[58,60]. In mice, restraint can induce catecholamine release and a parallel increase in PAI-1 production and gene expression[61,62].

Yamamoto et al. reported that only *Per1* mRNA expression was elevated in mouse peripheral tissues (liver, heart, and lung) by acute restraint stress[63]. *Per1* expression has a circadian rhythm in the SCN and in peripheral tissues. CLOCK-BMAL1-E-box, CREB-CREs, and glu-

cocorticoids-GRE pathways are considered important for *Per1* transcription. Furthermore, glucocorticoid signaling induced *Per1* gene expression without regulation of the central SCN clock. Tahara et al. also investigated the effects of restraint stress on circadian expression of clock genes in the SCN and peripheral tissues using Per2::LUC knock-in mice. Restraint stress in the evening or during the night, but not daytime, caused a phase-advance or -delay of circadian clocks in peripheral tissues (kidney, liver, submandibular gland), but not in the SCN[64]. Furthermore, this phase-shift disappeared with long-term exposure to repeated stress.

3. Social/psychological stressors

Many animal models have been established to evaluate the biological responses to social and psychological stressors. We previously reported that social isolation stimulated a stress response in mice leading to an increase in plasma corticosterone after 2 days' exposure, followed by a disrupted hepatic lipid metabolism-related pathway at 30 days' exposure, and increased risk of overweight with hepatic hypertrophy at 90 days' exposure[20,65,66]. Isolation stress can also result in the release of catecholamines and decreased levels of melatonin[67,68]. Forced swimming is another stressor used as a behavioral model for evaluation of antidepressant-like effects[21]. In various rat strains, forced swimming enhances secretion of ACTH, glucocorticoids, catecholamines, and prolactin[69-72]. Many reports have also suggested that melatonin exhibits anti-depressive activity against the forced swim stressor[73,74].

Social rejection and social hierarchy are stressors in humans and rodents. Good models for these social interactions include social defeat (SD) and social disruption, also referred to as the resident-intruder stress model[75]. There are many methods for investigating this stressor, including the housing of a rodent with an intruder, or an aggressive, older, dominant rodent, causing the establishment of a social hierarchy and/or fighting condition[76]. Many studies report that circulating corticosterone is enhanced by these stressors, including increased levels of catecholamines[77-79]. These stressors also have effects on the immune system, including an enlarged spleen, increased numbers of splenic immune cells, and the elevation of inflammatory cytokines[77,79]. These social and psychological stressors can also alter circadian rhythms, including a large reduction in the amplitude of the circadian rhythm of heart rate and body temperature[80].

Interestingly, daily body temperature rhythms were changed by a single SD in rats, while locomotor activity was less affected[81]. Repeated SD, involving a 30-min daily confrontation for 5 consecutive days, caused a decrease in the amplitude of circadian rhythms for heart rate and core body temperature[82]. Chronic subordination stress (CSS) in mice, which consists of inescapable defeat and chronic housing with an aggressor, increased food conversion efficiency, adrenal weight, and plasma corticosterone concentrations compared with controls, while a change in rhythmic locomotor activity was not observed. However, in Per2::LUC knock-in mice, CSS induced a phase advance in both the adrenal gland and pituitary[30].

Repeated SD can also alter behavioral, physiological, and immunological parameters depending on the time of day of stressor exposure. For example, physiological parameters such as adrenal gland weight and adrenal ACTH responsiveness were more affected by SD during the light phase, while immunological parameters such as IFNγ secretion were more affected by SD in the dark phase[83]. Furthermore, repeated SD in PER2::LUC mice caused alterations in the rhythm amplitude and expression of clock gene mRNA in the SCN and adrenal gland. Repeated SD during the dark phase, but not the light phase, also affected PER2::LUC rhythm in the SCN. Plasma brain-derived neurotropic factor (BDNF), which is highly expressed in the hippocampus, and BDNF mRNA levels in the SCN were increased in mice exposed to repeated SD during the light phase. Furthermore, it was suggested that central molecular clock rhythmicity is affected by repeated SD during the dark phase, while the adrenal peripheral clock is affected mainly by repeated SD during the light phase[84]. Body temperature and activity as output of the biological clock were affected by repeated SD during the dark phase. Such an effect was blocked in *Per1/2* mutant mice[85]. Finally, Tahara et al. reported that other types of stressors such as elevated platform stress and SD induced phase shifting of peripheral clocks in *Bmal1-Eluc* mice, as observed in mice exposed to restraint stress[64]. These data suggest that physical and psychological stress can potently entrain peripheral clocks through rapid endocrine response.

4. Chronic mild/unpredictable stressor

The chronic mild/unpredictable procedure consists of various mild stressors such as food or water deprivation, overnight illumination, reverse light/dark cycle, space reduction, or 45° cage tilt for several weeks. This type of stressor is considered a reliable animal model of depression. Distinct and prolonged disturbances of the diurnal and circadian rhythms of the locomotor activity was shown in rats exposed to this stressor[86]. BDNF plays an important role in the maintenance of neurons and in synaptic plasticity. However, the normal circadian variations in hippocampal BDNF expression and cell proliferation were not observed in depressed mice[87]. This mild stressor also induces depressive-like behavior and reduced amplitude of PER2 rhythm in the SCN in rats, and although the rhythm recovered to control levels after 2 weeks, the depressive-like behavior remained unchanged[88]. In mice exposed to this stressor, phase-shifted serum corticosterone levels and altered expression of circadian clock genes (*Clock, Bmal, Per1, Cry1*) was observed in the liver, but not in SCN[89].

5. Unexpected sudden stressor

Excessive geophysical impulse, for example a natural disaster such as an earthquake, is an example of an unexpected sudden stressor. Montenegro et al. subjected mice embryos to an earthquake-like stress using a vibrator cage, which resulted in an increase in cleft palates, potentially due to increased cortisone levels[90]. Liu et al. reported that unexpected earthquake-like shaking of mice induced a rapid increase in heart rate with simultaneous reduction of heart rate variability[91]. Moreover, in humans, exposure to a major disaster was reported to disrupt the circadian rhythm of blood pressure, especially increased morning blood pressure[92], which may partially account for the increasing onset of cardiovascular events during the sleep and morning periods[93]. Additionally, geophysical impulses can increase thrombophilic tendency and blood pressure, both of which can trigger cardiovascular events such as stroke and cardiac events. Furthermore, mice that experienced a simulated devastating earthquake including aftershocks in the laboratory animal room, displayed an elevation of serum corticosterone levels, a marked increase in food consumption without body weight gain, stimulation of anxiety behavior, and greater tone- and context-dependent conditioned freezing compared with mice pre-earthquake[94]. These animals also exhibited a disturbance in circadian rhythm pattern, which was delayed by approximately 9 h after the earthquake, indicating that an excessive stressor can affect biological circadian rhythms and evoke symptoms akin to 'jet lag' [95,96]. However, it is extremely difficult to distinguish whether this stressor is physical or psychological in mice.

6. Sleep disruption and biological rhythms

Sleep disruption, such as short sleep duration and disruptions due to shift work, is also a typical stressor, and was reported to reduce the circadian regulation of transcription and translation of clock genes in the brain (cerebral cortex) and in peripheral organs[97,98]. Although the physiological mediators of the effects of sleep disruption have not been established, altered food intake, changes in hormones such as glucocorticoids, and alterations in body temperature may be important. Indeed, as reported in the review by Archer and Oster[99], these biological stress responses are thought to underlie the established adverse health outcomes associated with sleep disruption such as metabolic syndrome and cancers.

Conclusion

People cope with high levels of stress in modern society, and are unconsciously exposed to various stressors complexed with physical, biological, chemical and social/psychological factors. Exposure to such non-specific stressors can induce specific biological responses, termed general adaptation syndrome, that develop in three stages (alarm reaction, resistance stage, and exhaustion stage). Rapid endocrine responses to the stressor during the alarm reaction period, for example glucocorticoid and catecholamine secretion into the bloodstream, provide the initial stress response. Such responses are necessary for the 'fight-or-flight' response, and often must occur rapidly for the organism to survive. Importantly, the majority of biological events including endocrine responses exert typical circadian rhythms, while disruption of circadian biological events is now thought to contribute to numerous diseases, including psychological disorders, immunopathy, serious disorders of the eye, and incidence of metabolic syndrome including obesity, type 2 diabetes, and dyslipidemia. There is also increasing evidence that exposure to stressors can alter the amplitude and/or cycle of circadian rhythms, and consequently aggravate and/or initiate various diseases including hypoinsulinemia and diabetes. Hence, studying the effects of circadian rhythms on biological responses against stressors is important for improving our understanding of biological rhythm-related illnesses.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

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