Proceedings of ICEGEE 2025 Symposium: Sensor Technology and Multimodal Data Analysis
DOI: 10.54254/2753-8818/110/2025.AU22984

The Effects of Circadian Rhythm Disorders on Hormones

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Abstract: The circadian rhythm is an autoregulatory feedback loop that occurs in the suprachiasmatic nucleus of the hypothalamus. It regulates various metabolic activities in the body, with processes controlled at specific times throughout the 24-hour cycle. This feedback loop involves the binding of genes and proteins, maintaining the body's biological clock. However, in modern times, circadian rhythms can often become misaligned due to factors like work schedules or internal issues. Hormones, which can be lipids or proteins, act on target cells to trigger various activities within the body. The types of hormones directly controlled by the circadian rhythm will be introduced in the following review. Additionally, we will discuss the consequences of circadian disruption on these hormones and the associated problems. This review systematically examined the fundamental principles of circadian rhythms, their molecular and neural regulatory mechanisms, and their critical role in governing endocrine functions, including the regulation of cortisol, insulin, leptin, and melatonin secretion.

Keywords: Circadian rhythm, Hormones, Circadian disruption

1. Introduction

The circadian rhythm regulates the biological functions of organisms during a 24-hour cycle and is affected by daily environmental variations [1]. They are vital in controlling periods of wakefulness and sleep, as well as the execution of essential processes, including hormone secretion and body temperature regulation [2]. There are various types of circadian rhythm disorders, including shift work disorders, jet lag, and affected sleep phase (**Table 1**).

Table 1: Types of circadian rhythm disorders

Disorder type	Prevalence	Risks
Delayed sleep phase disorder	Teenagers	Irritability, learning difficulties, behavioral problems [3]
Advanced sleep phase disorder	Elderly	Cognitive decline [4]
Shift work	Shift workers	Sleepiness during the day, memory affected
Jet lag	Air travelers who go to different time zones	Fatigue

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Intrinsic disorders occur naturally; they may be caused by genetic factors or chronic changes in the biological clock. On the other hand, extrinsic disorders comply with one's schedules, so they differ significantly between individuals; these are caused by changes in the external environment [5]. There are two types of intrinsic disorders, the delayed sleep disorder is basically found in teenagers and continues into adulthood. It is an abnormal delay of a major sleep episode as compared to the natural dark phase [6]. The other one refers to the symptoms of waking up too early. Shift work, such as the night shift, requires individuals to work during the dark hours and sleep during the day. Jet lag happens to people who travel across different time zones, where they usually feel exhausted or suffer other physical effects. Overall, both intrinsic and extrinsic disorders are sleep disorders triggered by a mismatch in the external environment with the endogenous sleep-wake cycle or changes in the circadian timekeeping system. As a result, people often experience abnormal sleepiness and wakefulness in the 24-hour light-dark cycle, such as insomnia or daytime sleepiness [5].

Hormones are substances, usually proteins and lipids, that are important for metabolic activities. For example, leptin regulates human energy homeostasis [7]. Both insulin and glucagon are responsible for controlling the blood glucose concentration through a negative feedback mechanism. For reproduction of organisms, follicle-stimulating hormone and luteinizing hormone both act in the ovulatory cycle [8]. Cortisol is a type of steroid hormone that controls immunity, stress, and metabolic functions. Like adrenaline, it is secreted by the adrenal glands. Noninfectious diseases such as Cushing's syndrome and Addison's syndrome are caused by an excess or a lack of cortisol [9]. Melatonin is a hormone that is closely related to the circadian rhythm. They are produced by the pineal glands in the dark hours, indicating the light-dark cycle to different parts of the body. They also stabilize the functions closely connected with the circadian rhythm, like sleep-wake rhythms and core temperature [10]. The human growth hormone's effects are wide, from physical and mental development to regulations in macromolecules that are important for metabolic functions and immunity [5]. The key purpose of this review is to explore and investigate the impact of different types of circadian rhythm disorders on the regulation of various hormones and their corresponding metabolic activity; also, the consequences that circadian rhythms bring to the hormones and the physical problems that come along with them will also be mentioned.

2. Background on circadian rhythms and hormonal systems

The master clock in organisms is located in the suprachiasmatic nucleus (SCN) of the hypothalamus. It functions by receiving light cues from the external environment and transmitting signals to other parts of the brain. The circadian rhythm is maintained through an autoregulatory feedback loop involving two key proteins: circadian locomotor output cycles kaput (CLOCK) and brain and muscle ARNT-like protein-1 (BMAL1) [11]. This loop operates on an approximately 24-hour cycle. In addition to regulating the central rhythm, the master clock also coordinates peripheral clocks throughout the body. Several hormones are directly regulated by the circadian rhythm, with their levels fluctuating across the 24-hour period to support various metabolic functions. For example, insulin, which lowers blood glucose levels by promoting its storage as glycogen in liver and muscle cells, is partly regulated by CLOCK and BMAL1. When these proteins bind to clock-controlled genes, they regulate insulin secretion and insulinotropic signal expression. Studies have shown that knocking out BMAL1 in mice impairs glucose uptake in skeletal muscles [11]. Cortisol, a glucocorticoid, promotes the breakdown of fats in adipose tissue and protein catabolism in muscle cells, releasing amino acids for metabolic use [12]. Its release is controlled by both neural and molecular mechanisms. Neural projections stimulate corticotropin-releasing hormone (CRH), which signals the pituitary gland to secrete adrenocorticotropic hormone (ACTH), subsequently triggering cortisol release from the adrenal glands. Additionally, CLOCK and BMAL1 can bind to the promoter region of the steroidogenic acute regulatory protein (StAR), regulating the rate of steroidogenesis. In humans,

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cortisol levels peak between 7 a.m. and 8 a.m. and decline throughout the day, reaching their lowest levels around midnight. Luteinizing hormone (LH) also exhibits circadian regulation. In mice, LH levels peak during the dark phase, aligning with their active period. BMAL1 plays a significant role in reproductive function. Female mice lacking BMAL1 do not exhibit LH surges, and although they still ovulate, they show reduced fertility due to lower progesterone levels during embryonic development [12]. In male mice, BMAL1 knockout leads to complete infertility, possibly due to disruptions in olfactory signaling pathways that are essential for mating behavior. Melatonin is another hormone directly influenced by the light-dark cycle. It regulates various metabolic activities in alignment with environmental light cues. In humans, melatonin secretion increases during the night, with peak levels occurring between 2 a.m. and 4 a.m. [11].

3. Effects of circadian rhythm disorders on hormone regulation

Since certain hormones are directly regulated by the circadian rhythm, disruptions in this cycle can lead to adverse health effects due to hormonal secretion occurring at inappropriate times of the day. Extrinsic circadian rhythm disorders, such as those caused by shift work, can significantly impact hormonal balance. Shift workers often experience physical health problems as a result of misaligned circadian timing, primarily due to alterations in melatonin secretion. Exposure to bright light during nighttime hours delays melatonin release, as light suppresses its production. Melatonin plays a critical role in regulating body temperature by initiating physiological processes that lower core temperature at night, thereby promoting sleep. When melatonin secretion is inhibited, these thermoregulatory processes are disrupted, leading to sleep disturbances. Furthermore, this inhibition affects cortisol production, which is regulated by the hypothalamic-pituitary-adrenal (HPA) axis. Normally, cortisol levels rise in the early morning as melatonin declines. However, when melatonin remains elevated due to delayed suppression, it interferes with this rhythm, contributing to impaired glucose metabolism, insulin resistance, and reduced glucose tolerance [3]. Other hormones involved in energy balance and homeostasis, such as leptin and ghrelin, are also affected. Leptin signals satiety after food intake, while ghrelin stimulates appetite and reduces fat oxidation. Sleep deprivation has been linked to elevated ghrelin levels [3], which can lead to increased food intake and contribute to weight gain and metabolic dysregulation. Another example of an extrinsic disruption is intermittent fasting, where individuals delay or skip regular eating times. Unlike shift work, intermittent fasting can have beneficial effects on circadian rhythm and metabolism. It increases insulin sensitivity and enhances the utilization of glucose and lipids for energy. Additionally, it promotes mitochondrial efficiency and supports DNA repair, contributing to healthier metabolic function and reduced biological aging [3]. For individuals affected by extrinsic circadian rhythm disorders—such as shift workers and older adults—melatonin replacement therapy is often recommended to restore hormonal balance and reduce the risk of associated metabolic diseases.

4. Conclusion

The circadian rhythm is closely linked with the fluctuations of hormone levels in the body. Their relationship is found to be intricate either in a cause-and-effect way or in a way that affects each other mutually. A change in the circadian rhythm can cause significant disorder, leading to various metabolic problems. The neuroendocrine system affects almost the whole body, and its problems shall not be neglected, as they may cause serious damage to health. Even though the external environment may require people to do activities that do not align with the 24-hour light-dark cycle, they should have enough awareness of the potential harm that these disorders may bring to them in the future and adjust their activities throughout the day accordingly. Moreover, people should also be aware of the effects of these disorders on vulnerable populations, and it is best to remind them of the

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harms the neuroendocrine disorders caused by circadian rhythm disruptions may bring to avoid more serious problems for their health.

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