Adrenal Glucocorticoid Rhythmic Secretion and Major Regulatory Factors Postprint

Authors: Fan Zhiyong, Qinhua Wang, Zhang Guanglei, Wu Xin, Hongnan Liu

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Abstract

In the process of maintaining internal homeostasis and adapting to the external environment, various physiological functions and metabolic activities in an organism undergo cyclical rhythmic changes in a certain temporal sequence, which is referred to as biological rhythms. As a core endocrine hormone for maintaining homeostasis, adrenal glucocorticoids play a crucial role in preserving the orderliness of vital activities and nutrient metabolism within the organism. Under natural conditions, external regulatory factors (such as food and light) act through complex synchronized feedback regulation between the suprachiasmatic nucleus of the hypothalamus and the biological clock to endow the production, secretion, and biological effects of adrenal glucocorticoids with rhythmic characteristics. This article primarily reviews the characteristics of rhythmic changes in the synthesis, secretion, and intrinsic mechanisms of action of glucocorticoids, aiming to provide references for research on biological rhythm mechanisms in organisms and their guidance for animal production.

Full Text

Rhythmic Secretion and Main Control Factors of Adrenal Glucocorticoid

WANG Qinhua[1],[2], ZHANG Guanglei[1],[2], LIU Hongnan[2], FAN Zhiyong[1], *WU Xin*[1],[2]

[1]College of Animal Science and Technology, Hunan Agricultural University, Changsha 410128, China
[2]Institute of Subtropical Agriculture, Chinese Academy of Sciences, Changsha 410125, China

Abstract

Biological rhythms are cyclical variations in physiological functions and metabolic activities that occur in a time-dependent manner to maintain internal homeostasis and adapt to external environments. As a core endocrine hormone, adrenal glucocorticoid plays a crucial role in maintaining the orderly occurrence of life activities and nutrient metabolism. Under natural conditions, exogenous control factors such as food and light rhythmically regulate glucocorticoid synthesis, secretion, and biological effects through complex synchronous feedback between the suprachiasmatic nucleus (SCN) in the hypothalamus and the circadian clock system. This review synthesizes current knowledge on the rhythmic characteristics of glucocorticoid synthesis and secretion and their underlying mechanisms, providing insights for research on biological rhythm mechanisms and their applications in animal production.

Keywords: biological rhythms; adrenal glucocorticoid; glucocorticoid; biological clock

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Glucocorticoid (GC), also known as adrenal glucocorticoid, was named for its initial discovery regulating blood glucose levels. GC secretion is primarily controlled by the hypothalamic-pituitary-adrenal (HPA) axis via related neurotransmitter receptors and exhibits autoregulatory negative feedback, making its concentration critical for maintaining homeostasis. GC secretion displays characteristic circadian rhythmicity, peaking between 08:00–10:00 daily and gradually declining to its lowest level at 24:00. Research indicates that this rhythmic pattern is primarily achieved through molecular regulation of adrenal clock genes under stimulation from external zeitgebers, while GC itself can attenuate food-induced phase shifts in peripheral circadian clocks, leading to inductive changes in circadian rhythms. This demonstrates a clear feedback interaction between GC secretion and biological rhythms, with exogenous control factors (food, light, etc.) playing important roles in regulating both adrenal GC secretion and circadian control, providing theoretical foundations for livestock production.

1. Main Biological Characteristics of GC

GC reaches target cells via the bloodstream, first binding to receptor proteins on the cell membrane to induce adenylate cyclase (AC) activity. In the presence of magnesium ions (Mg^{2+}), AC converts adenosine triphosphate (ATP) into the second messenger cyclic adenosine monophosphate (cAMP). Upon entering cells, GC binds to glucocorticoid receptor α (GRα) in the cytoplasm, forming a GC-GRα complex that subsequently binds to glucocorticoid response elements (GRE) on chromosomes to initiate or inhibit downstream gene expression and protein synthesis. Studies have confirmed that GC exerts its biological effects through both direct and indirect pathways. The direct pathway involves GC-cGR complexes directly regulating transcription of cytokine mRNAs such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-2

(IL-2). The indirect pathway involves anti-inflammatory and immunosuppressive processes through interactions between GC and other nuclear transcription factors.

GC exhibits extensive physiological functions in maintaining homeostasis and regulating metabolism. It effectively promotes gluconeogenesis and glycogen synthesis while inhibiting aerobic and anaerobic glycolysis. Regarding protein metabolism, GC enhances proteolytic enzyme activity, causing protein degradation in various tissues (lymph, muscle, skin, bone, connective tissue) and resulting in negative nitrogen balance. Furthermore, GC effects are significantly influenced by dose levels, showing clear dose-response relationships, with high levels primarily manifesting anti-inflammatory, anti-shock, and anti-toxic effects.

2. Rhythmic Secretion of Adrenal GC

In nature, organisms exhibit rhythmic phenomena in their life activities to adapt to environmental changes, known as biological clocks or circadian rhythms. The autonomous period of these clocks is approximately 24 hours, hence termed circadian clocks. In mammals, circadian rhythms are regulated by both the suprachiasmatic nucleus (SCN) in the hypothalamus and peripheral oscillators. The molecular basis of biological rhythms consists of specific, conserved core components. Master clock genes encode core elements including Circadian Locomotor Output Cycles Kaput (Clock), Brain and Muscle Arnt-like Protein-1 (Bmal1), Period (Per1, Per2, Per3), Cryptochrome (Cry1, Cry2), and Reverse Erythroblastosis Virus α (Rev-erbα) genes and their protein products. Clock and Bmal1 proteins initiate clock gene expression, while Cry and Per proteins provide negative feedback to block or attenuate this expression. The primary regulatory mechanism involves both positive and negative control, with GC regulation coupled to this process as shown in Figure 1 [Figure 1: see original paper].

Clock and Bmal1 form basic helix-loop-helix dimers that bind to E-box elements in clock gene promoters to activate transcription of Per, Cry, and Rev-Erba genes. As Per protein levels increase, they form complexes with Cry proteins and CKIE/MAPK-phosphorylated proteins. Differentiated embryo-chondrocyte expressed gene (DEC) competes with Clock-Bmal1 heterodimers for E-box binding, thereby inhibiting Clock-Bmal1 activity. In adrenal zona fasciculata cells, the master clock is initiated in the cytoplasm, and through feedback gene expression, hormone transcription occurs rhythmically in the nucleus. Subsequently, feedback genes Per and Cry inhibit master clock regulation, suppressing adrenal hormone production. When coupling between core and peripheral clocks is disrupted, the internal clock system readjusts to achieve a new equilibrium, influencing downstream gene expression, hormone secretion, metabolic responses, energy balance, and behavioral activities.

GC secretion exhibits circadian rhythmicity, with lowest levels at midnight and highest levels in early morning. During stress, endogenous GC secretion

can surge to approximately ten times baseline levels. Both GC secretion and its cellular actions depend on rhythmic release of adrenocorticotropic hormone (ACTH), which is controlled by the SCN. Studies on curcumin effects in chronically stressed rats demonstrated that compared to controls, stressed rats exhibited thickened adrenal cortex, atrophied medulla, and significantly reduced peripheral white blood cell counts (including decreased percentages of lymphocytes, monocytes, and neutrophils). These findings indicate that during stress, the SCN regulates HPA axis control of ACTH secretion, thereby modulating rhythmic GC secretion. Moreover, GC effectively influences expression of circadian clock genes and clock-controlled genes in peripheral tissues. Experiments with Per2/Cry1 double-mutant mice revealed defective HPA axis regulation, ultimately leading to metabolic disorders. Thus, when homeostasis is disrupted, the SCN controls rhythmic adrenal GC secretion to reestablish equilibrium and maintain orderly life activities.

Additionally, GC secretion rhythmicity is closely related to circadian clock gene expression, which plays a critical role in generating and maintaining GC circadian rhythms. Among endocrine signals, GC represents the most important timing cue for peripheral oscillators, enabling rhythmic secretion of metabolic hormones through adrenal clock peaks. For example, the circadian rhythm of corticosteroid secretion is achieved through rhythmic ACTH secretion from the SCN. This demonstrates that GC secretion is rhythmic and dependent on coordinated regulation by both the master clock and peripheral adrenal clocks.

3. Main Control Factors of Rhythmic GC Secretion and Applications

Light and food are crucial zeitgebers for biological rhythms. Light serves as the primary zeitgeber for the master clock. In mammals, retinal cells receive light signals and convert them into neural signals transmitted to the SCN, synchronizing the biological clock with the environment. Cryptochromes are flavoproteins widely present in higher eukaryotes that are sensitive to blue and near-ultraviolet light (UV-A/blue-light receptors) and participate in regulating GC rhythmic secretion. GC must bind to GR to exert effects, and recent studies have revealed that Cry can interact with GR to regulate glucose metabolism. Light stimulation experiments in mice showed that blood GC levels remained unchanged during the first 30 minutes but increased significantly between 60–120 minutes, returning to baseline after 180 minutes. This demonstrates that light stimulation induces rhythmic fluctuations in GC secretion, with life activities exhibiting hierarchical changes. Under sunlight stimulation, GC secretion develops circadian rhythmicity to adapt to external environmental changes (sleep-wake cycles). Genetic deletion of Cry1 and Cry2 causes glucose intolerance and elevated cortisol levels, indicating that GC level increases are regulated through different mechanisms: light-induced GC secretion is likely controlled by the circadian system, while gene deletion-induced changes may involve both master and peripheral adrenal clocks. Conversely, GC fluctuations can cause phase shifts in peripheral oscillators that feed back to the master clock.

Food intake also significantly affects GC secretion in mammals, with both feeding and fasting states influencing GC levels. GC secretion and circadian regulation are both controlled by the SCN via the HPA axis and other pathways. As an important stimulus, food can suppress food-induced peripheral circadian oscillators. Researchers found that when mice were fed during daytime, corticosterone levels were very high, which is crucial for reducing blood glucose during daytime feeding. Some scientists propose that peripheral oscillators dominate during feeding, and GC can suppress phase shifts induced by food in peripheral circadian oscillators.

The primary role of rhythmic GC secretion is maintaining energy homeostasis. Many glucose homeostasis pathways have side effects, such as metabolic diseases closely related to GC secretion. In livestock production, dynamically adjusting energy intake according to different physiological or feeding stages to match hormonal rhythmicity can achieve feed savings and efficient utilization. The circadian clock controls daily GC secretion rhythms through both master clocks and adrenal clocks—the corticosterone circadian gating mechanism. The adrenal gland possesses its own clock that closely links with peripheral clocks, which rhythmically control steroid production through GC physiological rhythms. In Bmal1 knockout mice, the adrenal clock could still produce corticosterone, but behavior was significantly affected, with altered Per1 expression but unaffected Per2. Researchers conclude that peripheral adrenal clocks play important roles in mammalian physiological coordination through rhythmic GC secretion. Thus, GC rhythmicity emerges from coordinated regulation by zeitgebers, master clocks, and peripheral oscillators, as illustrated in Figure 2 [Figure 2: see original paper].

In production practice, controlling light and food can regulate livestock performance. For instance, administering growth promoters during peak GC secretion periods may enhance production efficiency. The relationship between nutritional effects and GC rhythmicity—such as which pathways regulate GC rhythmic secretion in response to specific nutrients—requires further investigation. Recent studies show that feeding different crude protein diets at different times can improve growth performance and blood biochemical indices in pigs. However, the mechanisms linking nutrient metabolism regulation to GC secretion rhythms and the relationship between GC rhythmicity and animal nutritional requirements need further research.

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Note: Figure translations are in progress. See original paper for figures.