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Review

Circadian rhythm of adrenal glucocorticoid: Its regulation and clinical implications

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ABSTRACT

Glucocorticoid (GC) is an adrenal steroid hormone that controls a variety of physiological processes such as metabolism, immune response, cardiovascular activity, and brain function. In addition to GC induction in response to stress, even in relatively undisturbed states its circulating level is subjected to a robust daily variation with a peak around the onset of the active period of the day. It has long been believed that the synthesis and secretion of GC are primarily regulated by the hypothalamus–pituitary–adrenal (HPA) neuroendocrine axis. However, recent chronobiological research strongly supports the idea that multiple regulatory mechanisms along with the classical HPA neuroendocrine axis underlie the diurnal rhythm of circulating GC. Most notably, recent studies demonstrate that the molecular circadian clockwork is heavily involved in the daily GC rhythm at multiple levels. The daily GC rhythm is implicated in various human diseases accompanied by abnormal GC levels. Patients with such diseases frequently show a blunted GC rhythmicity and, more importantly, circadian rhythm-related symptoms. In this review, we focus on recent advances in the understanding of the circadian regulation of adrenal GC and its implications in human health and disease.

1. Introduction

Circadian rhythms are comprised of a ubiquitous biological oscillation of approximately 24-h periods that are highly conserved from cyanobacteria to humans. This daily rhythm is not a simple response to alternating changes of day and night. It arises from an innate and genetically operated timekeeping system referred to as a "biological clock" [1,2]. This internal timekeeping system allows organisms to anticipate and prepare for changes in their physical environments, thereby enabling them to behave appropriately at the right time of day. The biological clock also greatly contributes to ensuring that certain physiological processes take place in coordination with others [3]. In mammals, the suprachiasmatic nucleus (SCN) of the anterior hypothalamus functions as the master circadian pacemaker, driving overt circadian rhythms such as the rest-activity cycle, daily variations in metabolism and body temperature, and the rhythmic secretion of hormones [4].

Glucocorticoid (GC) is an adrenal steroid hormone that plays a crucial role in the adaptive responses to various types of stress and is under the control of the hypothalamus–pituitary–adrenal gland (HPA) neuroendocrine axis. In addition to its stress reactivity, robust daily variation in the circulating level is another key feature of this hormone. It is widely accepted that the daily GC rhythm is also under the control of circadian timing because its rhythmicity is completely blunted by disruption of the SCN harboring the master oscillator [5]. It is well known that chronic dysregulation of GC, i.e. either hyper- or hyposecretion, induces the onset of diverse pathological conditions by disrupting carbohydrate and lipid metabolism, immune response, cardiovascular activity, mood, and cognitive/brain functions. A growing body of evidence suggests that not only the level of circulating GC but also its rhythmic activity plays a significant role in human health and disease [6,7]. Therefore, understanding the regulatory mechanisms of the daily GC rhythm and its physiological relevance can provide novel insight into both the molecular basis and clinical treatment of human diseases involving abnormal GC secretion. Here, we review recent progress in circadian clock research and focus on the roles of the circadian timing system in the daily GC rhythm and its clinical implications.

2. Circadian timing system and molecular clockwork

2.1. The mammalian circadian clockwork

Because of the earth's rotation, almost all organisms function under 24-h day–night cycles. To adapt to and anticipate external daily cycles, organisms have evolved an internal timekeeping system. This daily timekeeping system is referred to as the "circadian clock" from the Latin "circa diem," which literally meaning "approximately a day." It is both autonomous and self-sustainable but is also continuously entrained by external time cues called "zeitgeber." The mammalian circadian timing system consists of 3 basic components: 1) input signals (environmental cues), 2) a circadian oscillator as an intrinsic

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rhythm generator and 3) output rhythms. The hypothalamic SCN has generally been considered to be the central circadian oscillator both anatomically and functionally; it receives photic information from the eyes via the retino-hypothalamic tract, and then synchronizes the circadian timing system with environmental time [4,8]. This notion is strongly supported by findings that selective ablation of the SCN leads to a complete loss of circadian rhythmicity, whereas transplantation of an intact SCN into arrhythmic mutant animals restores circadian rhythmicity [9,10]. The circadian rhythm generated in the SCN is believed to be converted into neuronal or hormonal signals that affect metabolic processes, physiology and behavior (Fig. 1).

The autonomous and self-sustaining nature of the circadian timing system primarily depends on the presence of a genetic mechanism known as the molecular circadian clockwork. "Clock genes" are required for the generation and maintenance of the circadian rhythm in an organism and even within individual cells [11,12]. The clock genes and their gene products cooperatively promote rhythmic gene expression by two interlocked positive and negative transcription/translation feedback loops that are core and auxiliary (Fig. 2). In the principal or core feedback loop, members of the basic helix–loop–helix–Period-ARNT-single-minded (bHLH-PAS) transcription factor superfamily, such as CLOCK and BMAL1, form heterodimers to activate the transcription of their target genes containing E-box elements in the *cis*-regulatory regions of those genes [13–15]. These target genes include their negative regulators such as the *Periods* (PERs: PER1, PER2 and PER3) and the *Cryptochromes* (CRYs: CRY1 and CRY2). The concentration of BMAL1 is adjusted by an auxiliary or stabilizing feedback loop formed by the clock-controlled nuclear receptors REV-ERBα and RORα [16–19]. The self-sustaining feedback loops described in Fig. 2 constitute the circadian molecular clock machinery in an approximate 24-h period.

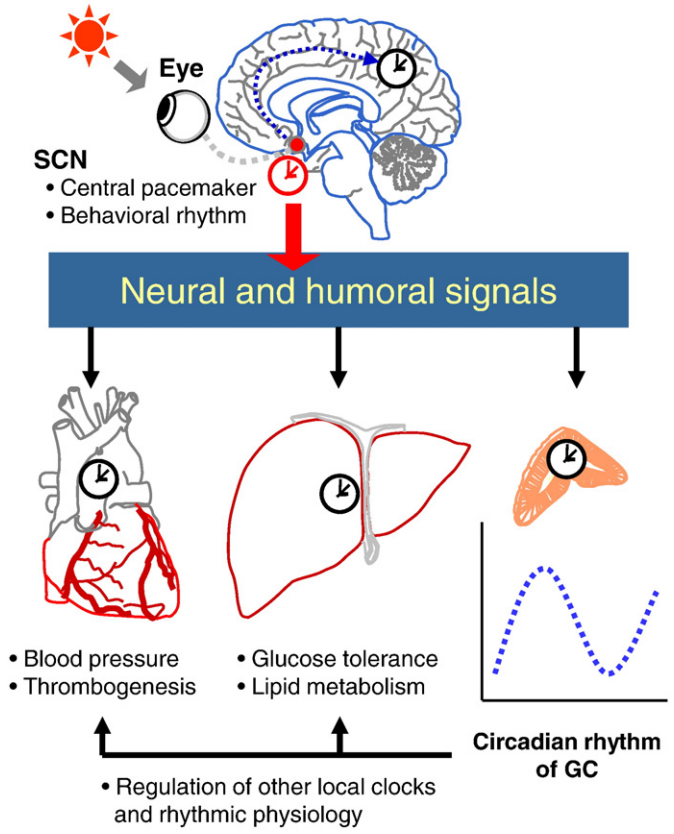

Fig. 1. Hierarchical organization of the mammalian circadian timing system. The suprachiasmatic nucleus (SCN), which resides in the ventral hypothalamus, functions as the central clock responsible for the coordination of multiple clock networks in the body. It communicates with and synchronizes local clockworks in other tissues, including both peripheral tissues and extra-SCN regions of the brain. Examination of the tissue-specific modulation of the clock machinery revealed the autonomous role of each local clock (also see the text), and the adrenal peripheral clock in particular is involved in the daily rhythms of GC and exerts an impact on the synchronization of other peripheral clocks and the regulation of physiological systems, including metabolism.

In addition to core regulation at the level of transcription/translation, circadian clock proteins are also subjected to extensive post-translational modifications that appear to control their protein stability, nuclear localization and functional activity. For example, casein kinase 1ε and δ are known to be critical factors that regulate the turnover of PERs and CRYs in mammals [20–22]. BMAL1 is rhythmically sumoylated *in vivo* and the sumoylation promotes its interaction with CLOCK, exclusive nuclear accumulation in promyelocytic leukemia (PML) nuclear bodies, transactivation and ubiquitin-dependent degradation [23–25]. BMAL1 is also regulated by acetylation so as to have a role in the maintenance of circadian rhythmicity [26]. In addition, the Ca^{2+}-dependent protein kinase C (PKC)-mediated phosphorylation of CLOCK and subsequent recruitment of cofactors to the CLOCK/BMAL1 heterodimer appear to be important for the phase resetting of the mammalian circadian clock [27,28]. Post-translational regulation of the clock proteins and its functional significance are extensively reviewed elsewhere [11,12].

2.2. Central and peripheral clocks in rhythmic physiological outputs

The mammalian circadian system is organized in a hierarchical manner. At the top of the mammalian circadian timing system, the SCN is composed of densely packed neurons that have self-sustaining rhythmic capacity [29]. It is striking that not only the SCN but also most tissues and peripheral organs express their own clock genes. It has been shown that even cultured cells *in vitro* retain their rhythmicity at the single cell level; thus, a high concentration of serum or synthetic GC agonist is able to synchronize individual rhythms so as to exhibit a robust cyclic clock gene expression at the cell population level [30–33]. Furthermore, it has been established that most mammalian cells possess their own circadian clocks. These clocks have a molecular makeup similar to that in SCN pacemaker neurons, but are referred to as peripheral or local clocks to distinguish them from the master clock in the SCN. Therefore, the SCN serves as the center for harmonizing the circadian rhythm in mammals by coordinating the rhythms of the peripheral clocks scattered throughout the body (Fig. 1). The SCN maintains continuous communication with the peripheral clocks through a variety of neural and humoral signals [34]. In addition to the time information transmitted by the SCN, other zeitgebers, such as feeding times and body temperature rhythms, play an important role in the resetting of these peripheral timekeepers [4]. In this context, it should be noted that GC is an attractive candidate for the key hormonal link between the SCN and the peripheral clocks. This issue will be discussed in a later section of the present article.

A variety of physiological processes in mammals, including the sleep–wake cycle, body temperature, renal plasma flow and cardiovascular activity are influenced by circadian regulation [3]. Although the rhythmic features of these physiological processes require SCN involvement, the presence of ubiquitous peripheral oscillators strongly supports their contribution to the manifestation of circadian rhythms in a variety of cellular processes. Considerable evidence has been obtained from transcriptome-profiling studies. For example, 5–10% of all mRNA species display a circadian expression pattern in the liver [35–38]. A comparison of the transcriptome profiles in different tissues [38] revealed that most circadian transcripts are expressed in a tissue-specific fashion, which is in keeping with the idea that different functions are controlled by different tissues' own local circadian clockwork. However, the roles of the peripheral clocks and the central pacemaker in governing the circadian functions in a given organ are rarely distinguished. In this context, selective modulation of certain peripheral clock machinery has been recently examined for the