
Regulation of glucocorticoids by the central nervous system

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ABSTRACT

The central nervous biological CLOCK system (highly conserved and sophisticated molecular "clock"), under the influence of light/dark alterations, "creates" the internal circadian rhythms. The organisms "feel" these rhythmic external changes to synchronise their physical activities, including energy metabolism, sleep, and immune function. A number of immunological functions are dependent on influence of sleep on circadian rhythms, including the type and magnitude of immune responses following antigenic challenge. Loss of sleep, in turn, prevents these immunosupportive actions and alters the production of glucocorticoids during the night. Major life events lead to an intense release of stress response system mediators (mainly norepinephrine and cortisol), whereas in minor life events, only short-lived surges of these neurotransmitters and hormones are expected. The immune system reactivity follows circadian rhythms imposed by the CLOCK and sleep synchronisation, and is particularly altered in presence of chronic stress. As a consequence of the altered CNS-endocrine control, low-dose long-term glucocorticoid therapy in chronic rheumatic diseases is today considered as a "hormonal replacement therapy" to supplement the peripheral insufficiency of endogenous glucocorticoids in modulating the immunel/inflammatory reaction.

Introduction

All organisms live under the influence of circadian rhythms (day/night cycles) created by the 24-hour rotation of the planet. Organisms "feel" these rhythmic external changes and synchronise their physical activities, including energy metabolism, sleep and immune function, in order to increase their chances for survival by distributing bioenergies along 24 hours (1, 2). Therefore, organisms have devel-

oped a highly conserved and sophisticated ubiquitous molecular "clock," mainly focused on the central nervous CLOCK system, which "creates" the internal circadian rhythm under the influence of light/dark information (3) (Fig. 1).

In addition to synchronising their physical activities to day/night changes, organisms meet short- and long-term changes in the environment called "stressors," which can be external (e.g. trauma or invasion by microbes) or internal (e.g. interpersonal problems) (4). In order to react to the stressful stimuli, organisms have developed another regulatory system, the stress response system, which "senses" the environmental harmful stimuli and processes responsive signals in the central nervous system (CNS) (5). The stress response system consists of the hypothalamic-pituitary-adrenal (HPA) axis and its end-effectors glucocorticoids, and the locus coeruleus/norepinephrine-autonomic nervous systems and their end-effectors, norepinephrine and epinephrine (5) (Fig. 1).

The CLOCK and stress response systems are both fundamental for survival, and thus communicate with one another at multiple levels to adjust numerous physiologic adaptive responses.

Several immune parameters show circadian fluctuations over the 24-hour day. For example, circulating naive T-cells and production of pro-inflammatory cytokines peak during nighttime, whereas cytotoxic effector leukocytes in circulation and production of the anti-inflammatory cytokine IL-10 peak during daytime (6). These temporal changes originate from a combined influence of the circadian system and sleep. Sympathetic tone and cortisol levels show a circadian nadir during nighttime and are further suppressed by sleep, whereas growth hormone and melatonin show a circadian peak during nighttime and are further enhanced by sleep (7, 8) (Fig. 1).

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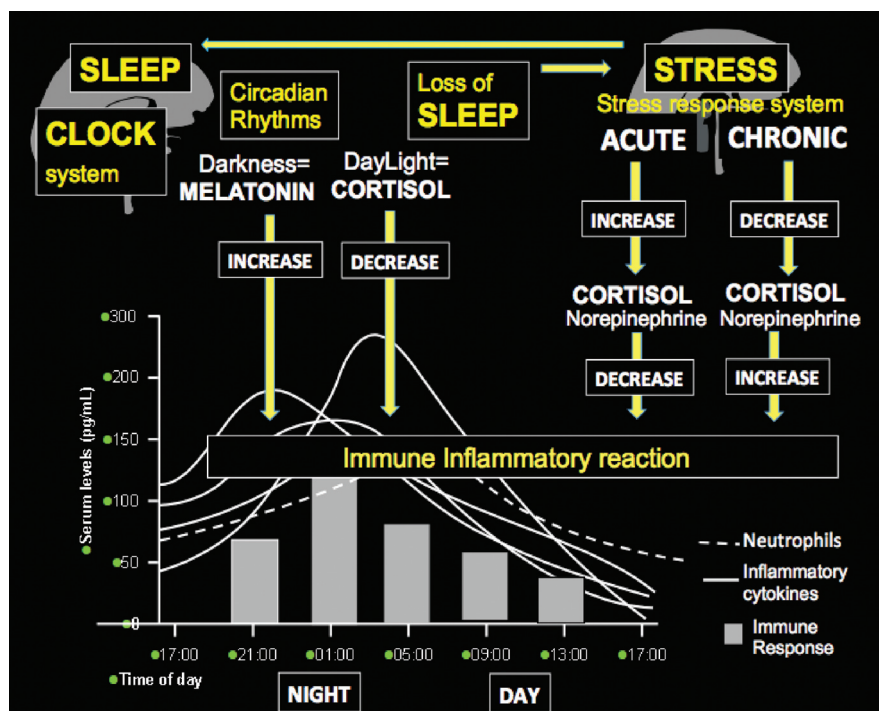


Fig. 1. Synchronisation between the CLOCK system and sleep is essential to maintain efficient CNS control over glucocorticoid (cortisol) night/early morning production. Melatonin, produced by the CNS during darkness, enhances the immune/inflammatory reaction. CLOCK and the stress responses system are both linked. Acute and chronic stresses modulate the immune/inflammatory reaction in different ways. Finally, the immune/inflammatory system reactivity (*i.e.* neutrophil activation, cytokine production) follows circadian rhythms imposed by the CLOCK and sleep synchronisation, and is altered in presence of chronic stress.

CLOCK system, sleep, cortisol and immune function

Light activates the central master of circadian daily rhythms located in the CNS and orchestrates the daily rhythmic release of glucocorticoids by influencing the central activity of the hypothalamus-pituitary-adrenal (HPA) axis. Therefore, circulating glucocorticoids fluctuate naturally in a circadian fashion (9).

Dysregulation or uncoupling of the cortisol circadian rhythm under the influence of the CNS CLOCK system, and local tissue sensitivity to glucocorticoids by the peripheral CLOCK, may induce a functional hypercortisolism in target tissues, which could be followed by development of pathologic conditions, including immune system dysregulation (10) (Fig. 1).

Classical causes of dysregulation of the cortisol circadian rhythm might appear in rotating shift workers, whose circadian system is repetitively reset by night-time activity/day-time sleep, or individuals exposed to fre-

quent jet lag travels over time zones. As a consequence, these subjects are at an increased risk for the development of various pathologic conditions, such as components of the metabolic syndrome or cardiometabolic disease and stroke, as well as early mortality that might result from such time-integrated increased target tissue exposure to glucocorticoids (hypercortisolism) (11). Similarly, interactions between the CLOCK system and the HPA axis also are observed in regulation of immune function. At least in humans, the CLOCK system produces circadian fluctuation of several cytokines, including interferon (IFN)-gamma, IL-1beta, IL-6, and TNF as well as of circulating T- and B-lymphocytes and natural killer cells (12, 13).

Indeed, knockout mice defective in components of the CLOCK system demonstrate various immune dysfunctions, such as a blunted and/or absent circadian rhythm in circulating leukocytes and cytokine secretion, an impaired response to lipopolysaccharide-

induced endotoxic shock, and defective B-lymphocyte development (3).

Activation of the HPA axis and subsequent release of glucocorticoids (both in acute and chronic condition) in turn strongly influence immune activity and the inflammatory reaction (8). A number of immunological functions are dependent on influence exerted by sleep on circadian rhythms including the type and magnitude of immune responses following antigenic challenge (14, 15). Loss of sleep, in turn, prevents these immunosupportive actions.

In addition to these impairments, prolonged sleep loss as induced experimentally, for example, by sleep restriction, produces a stress-like response (chronic-like) which immunologically is best characterised as inflammation with increases in leukocyte and neutrophil counts, cytokine serum levels and C-reactive protein (CRP) (16) (Fig. 1).

Candidates for the sleep deprivation effects are the stress hormones cortisol and epinephrine. Cortisol increases production, bone marrow release, intravascular half-life and demargination of neutrophils (17). Given that the enhancing effect of cortisol on neutrophil counts requires about 2 to 3 hours to emerge, it could well be that the acute nocturnal increase in cortisol during sleep restriction contributes to the neutrophilic response that was assessed in the following morning in a recent study (16, 17).

Epinephrine also mobilises neutrophils from the marginal pool even more efficiently and much faster than cortisol (17). Furthermore, sleep deprivation severely disturbs the functional rhythm of nT(reg) and CD4(+)/CD25(-) T cells (18). Other mediators that are known to be regulated by sleep, and the circadian system, including melatonin, prolactin, growth hormone, leptin, vitamin D and vasopressin, probably also contribute to the pro-inflammatory state of nocturnal sleep and the anti-inflammatory state of daytime activity (19).

In addition, balanced energy-rich fuel allocation normally aligned with circadian rhythms, appears primarily available for the immune/inflammatory reaction activated at night in chronic immune/inflammatory diseases (2, 20).

Melatonin opposed to cortisol as supporter of the circadian immune response during the night

Light, the environmental stimulus detected by the retina, adjusts the central CLOCK system in the suprachiasmatic nuclei, which innervate the pineal gland through a polysynaptic pathway. During the night, the pineal gland produces and releases the nocturnal hormone melatonin (MLT), which circulates throughout the whole body and adjusts several bodily functions according to the existence and duration of darkness (21). During the time frame of an inflammatory response, pro-inflammatory cytokines such as TNF-alpha inhibit, while anti-inflammatory mediators such as glucocorticoids enhance, the synthesis of MLT, interfering in the daily adjustment of the light/dark cycle implicating the darkness hormone MLT as a modulator of defense responses (22) (Fig. 1).

In 2002, our first study evaluated MLT levels in patients with rheumatoid arthritis (RA) with a focus upon analyses of circadian variations (23). MLT serum levels at 8 pm and 8 am were found to be significantly higher in patients with RA than in healthy controls. The differences were more evident in patients who were older than 60 years. MLT levels increased progressively from 8 pm to the early morning hours in both patients with RA and in healthy subjects; however, they reached peak levels at midnight in patients with RA, which was at least 2 hours earlier than in controls (23).

Subsequently, MLT concentrations in RA reached a plateau that continued for 2–3 hours; this was not observed in controls. The study confirmed that the nocturnal rhythm of MLT occurs also in patients with RA, but with an earlier peak and a broader plateau in the early morning.

In human peripheral blood mononuclear cells, at physiological concentrations, MLT has been reported to stimulate the production of IFN-gamma, IL-1, IL-2, IL-6 and IL-12, but not IL-4 (24, 25).

In addition, MLT was found to enhance production of inflammatory cytokines from cultured human monocytes/mac-

rophages, including IL-12 and turning the MLT/IL-2 connection towards the enhancement of T cell immunity (26). MLT was found to be detectable at high concentration in synovial fluids from patients who had RA, and binding sites for MLT were present in synovial macrophages (27).

IFN-gamma, IL-1, IL-6, IL-2, IL-12 and TNF-alpha production, (Th1 cytokines/promoting cytokines) reach their peak during the night and early morning, shortly after MLT serum levels are highest and plasma cortisol is lowest. These observations are consistent with a possibility that MLT up-regulates cytokine production and immune function (21).

Studies on experimental granulomatous lesions confirmed that the rhythm of the inflammatory reaction is due to the rhythmic MLT release by the pineal gland (21).

Therefore, MLT may activate the inflammatory response during the night, at least in RA, which is mainly considered to be a Th1 cytokine driven immune disease. Recently, TNF-alpha concentrations in the serum were found to be higher in northern European patients with RA than in control subjects, and were found to be significantly correlated with increased serum MLT concentrations, at least during the winter (28). Therefore, increased serum concentrations and circadian rhythm of MLT and a “relative adrenal insufficiency” in chronic RA (low cortisol), allows Th1 type cytokines to be produced in higher amounts during the late night under the enhancing effect of pineal hormone (1). A double blind placebo-controlled study investigating the effects of MLT administration in patients with RA confirmed a proinflammatory activity (29).

Stress effects on cortisol availability

Stress is recognised as an important risk factor in the pathogenesis of autoimmune rheumatic diseases (*e.g.* rheumatoid arthritis) by considering that the activation of the stress response system influences the close relationships existing between the HPA axis, the sympathetic nervous system and the immune system (5, 30).

The stress response results in the release of neurotransmitters (norepinephrine), hormones (cortisol) and immune cells which serve to send an efferent message from the brain to the periphery (31).

Major life events lead to an intense release of stress mediators (large time integral of released neurotransmitters and hormones), whereas in minor life events, only short-lived surges of neurotransmitters and hormones (cortisol) are expected. Therefore, it is suggested that neurotransmitters such as norepinephrine or stress hormones such as cortisol might have different effects on immune/inflammatory responses at high and low concentrations present during short or extended periods of time, respectively (Fig. 1). For example, long-lasting (chronic) stress may lead to proinflammatory effects because no adequate long-term responses of stress axes (antiinflammatory) are to be expected to downregulate the immune/inflammatory reaction (30) (Fig. 1).

Conclusions

Synchronisation between the CLOCK system and sleep is essential to maintain efficient the CNS control on glucocorticoid production during the night and health status. On the other hand, the CLOCK and the stress response system are both fundamental for survival, since they communicate with one another to adjust numerous physiologic adaptive responses (3). The final result of dysregulation or uncoupling of the CNS control (CLOCK and stress response system) on adrenal gland (HPA axis), results in reduced endogenous production and availability of glucocorticoids.

The immune system activity follows circadian rhythms imposed by the CLOCK and sleep synchronisation, and is altered in presence of chronic stress.

In conclusion, as a consequence of the altered CNS-endocrine control, low-dose long-term glucocorticoid therapy in chronic rheumatic diseases, is today considered as a “hormonal replacement therapy” to supplement the peripheral insufficiency of endogenous glucocorticoids in modulating the immune/inflammatory reaction (32).

Authors' contributions

M. Cutolo: drafting the paper, generating the figure, and final approval.

F. Buttgereit: discussing the contents, revising the draft, and final approval.

R.H. Straub: discussing the contents, revising the draft, and final approval.

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