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Circadian characteristics of permissive and suppressive effects of cortisol and their role in homeostasis and the acute inflammatory response

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ABSTRACT

In this work we explore a semi-mechanistic model that considers cortisol's permissive and suppressive effects through the regulation of cytokine receptors and cytokines respectively. Our model reveals the proactive role of cortisol during the resting period and its reactive character during the body's activity phase. Administration of an acute LPS dose during the night, when cortisol's permissive effects are higher than suppressive, leads to increased cytokine levels compared to LPS administration at morning when cortisol's suppressive effects are higher. Interestingly, our model presents a hysteretic behavior where the relative predominance of permissive or suppressive effects results not only from cortisol levels but also from the previous states of the model. Therefore, for the same cortisol levels, administration of an inflammatory stimulus at cortisol's ascending phase, that follows a time period where cytokine receptor expression is elevated ultimately sensitizing the body for the impending stimulus, leads to higher cytokine expression compared to administration of the same stimulus at cortisol's descending phase.

1. Introduction

Inflammation is a critical component of body's response to a variety of harmful stimuli such as infection and trauma. Under normal circumstances, the bi-directional flow of information between immune and neuroendocrine systems removes the pathogen or repairs the damaged tissue and restores homeostasis [1]. The principal peripheral effectors of the neuroendocrine system are glucocorticoids that are regulated by the hypothalamic– pituitary–adrenal (HPA) axis, and the catecholamines norepinephrine/epinephrine which are secreted by the sympathetic nervous system [2]. Mainly due to their immunosuppressive actions, glucocorticoids (cortisol in humans) have been regularly utilized for the treatment of autoimmune diseases and inflammatory disorders [3,4]. Glucocorticoids induce their anti-inflammatory action through suppressing the production of numerous pro-inflammatory mediators (cytokines) such as IL-1 (interleukin-1), IL-2, IL-3, IL-6, and IFN-γ (interferon-γ) which are dangerous in excess [5,6]. Along with their immunosuppressive role, it has long been suggested that they enhance the response to external stressors rather than solely limiting it [7]. Therefore glucocorticoids have been shown to up-regulate the expression of cytokine receptors [8–12] sensitizing the target cells to an upcoming stimulus. Interestingly, these opposing glucocorticoid effects do not cancel each other out, but are rather providing an optimal defense mechanism [13]. Investigation of the dynamics giving rise to glucocorticoids permissive and suppressive actions could provide insight into the emergent dynamics of response to stress.

Glucocorticoids exert their genomic effects through two types of receptors: *type I* (mineral corticoid receptor, MR), and *type II* (glucocorticoid receptor, GR) that after binding to glucocorticoid ligand, they translocate to the nucleus where they interact with specific promoter regions named glucocorticoid responsive elements (GREs) to activate appropriate hormone-responsive genes [14–16]. Since the affinity of MR to cortisol is much higher compared to that for GR [17], it has been hypothesized that lower cortisol levels mediate downstream effects mainly through MR while at higher cortisol concentrations binding to GR dominates [18,19]. In the context of immunity and inflammation, lower cortisol levels have been further shown to act proactively, thus enhancing resistance to infection [20,21] while suppressive actions are a characteristic of higher glucocorticoid levels [7].

We have previously presented a number of *in silico* studies of acute inflammation [22–27]. In the present work we further explore

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cortisol's dynamic behavior taking into consideration its inducing effect on pro-inflammatory cytokine receptors aiming to elucidate the balance between its suppressive and permissive effects. Particularly in the work herein, cortisol's permissive effects represent the MR-mediated induction of cytokine receptors whereas cortisol's suppressive effects represent the GR mediated suppression of cytokines. Furthermore, we account for circadian rhythmicity present both at the single immune cell level (periphery) by peripheral clock genes (PCGs) and at the systemic level of hormonal secretion.

Our model describes cortisol's antagonistic effects during the course of the day. Permissive effects are accentuated during the dark (rest) period where the body is building its defense for the impending activity phase whereas during the light (active) period immunosuppressive characteristics of cortisol are denoted [7]. Thus we predict that acute LPS administration at night results in higher levels of cytokines compared to LPS administration at morning time. Furthermore, our model indicates that increased cytokine receptor expression during the night, leads to a more potent inflammatory response when acute stimulus is administered at cortisol's rising phase compared to its descending phase even for the same cortisol values. This hysteretic behavior further illustrates cortisol's preparative role for either sensitizing or desensitizing the body.

2. Materials and methods

2.1. Modeling circadian rhythms at the systemic and peripheral level

2.1.1. Cortisol and glucocorticoid/mineralocorticoid receptors pharmacodynamics

The overall model is depicted in Fig. 1. At the systemic level we considered the daily secretion of cortisol (F) using the "two rates" model [24,25,28], where a zero-order production term (*RF*) is set to two different values simulating the increased cortisol production at morning and the lower production at the rest of the day (Eq. (1)). In Eq. (1), *mod* represents the remainder (modulo operation) of the division of time (t) with 24.

Subsequently, cortisol reaches peripheral cells (Eq. (2)) where it diffuses into their cytoplasm, and binds to the active forms of its two receptors (MR_c^* and GR_c^*). Similar to the model of [29] we hypothesize that cortisol activates, though phosphorylation, the two receptors [30,31] rendering them active and able to bind cortisol (Eqs. (3) and (6)). Following binding, the two glucocorticoid complexes (FMR_c Eq. (4), and FGR_c Eq. (7)) translocate into the nucleus ($FMR(N)_c$ Eq. (5), and $FGR(N)_c$ Eq. (8)) and ultimately binds to the GRE at the promoter regions of target genes (Per/Cry, cytokine receptors and cytokines) [32].

$$\frac{dF}{dt} = RF + k_{\text{in},F_{en}}(1 + k_{F_{en},P}P_{ens}) - k_{\text{out},F}F$$

$$RF = \begin{cases} 0, & 0 < \text{mod}(t,24) < t_{F1} \\ k_{\text{in,RF1}}, & t_{F1} < \text{mod}(t,24) < t_{F2} \end{cases} \quad (1)$$

$$\frac{dF_{\text{per,c}}}{dt} = \frac{1}{\tau}(F - F_{\text{per,c}}) \quad (2)$$

Mineralocorticoid receptor:

$$\frac{d\text{MR}_c^*}{dt} = \frac{k_{\text{MR}}\left(1 + \frac{k_{\text{F,MR}}F_{\text{per,c}}}{K_{\text{F,MR}} + F_{\text{per,c}}}\right)(\text{MR}_T - \text{MR}_c^*)}{K_{\text{MR}} + \text{MR}_T - \text{MR}_c^*} - \frac{k_{\text{MR,deg}} \cdot \text{MR}_c^*}{K_{\text{MR,deg}} + \text{MR}_c^*} - k_{\text{b,MR}}F_{\text{per,c}}\text{MR}_c^* + k_{\text{r,MR}}\text{FMR(N)}_c \quad (3)$$

$$\frac{d\text{FMR}_c}{dt} = F_{\text{per,c}}\text{MR}_c - \text{FMR}_c \quad (4)$$

$$\frac{d\text{FMR(N)}_c}{dt} = \text{FMR}_c - \text{FMR(N)}_c \quad (5)$$

Glucocorticoid receptor:

$$\frac{d\text{GR}_c^*}{dt} = \frac{k_{\text{GR}} \cdot \left(1 + \frac{k_{\text{F,GR}} \cdot F_{\text{per,c}}}{K_{\text{F,GR}} + F_{\text{per,c}}}\right) \cdot (\text{GR}_T - \text{GR}_c^*)}{K_{\text{GR}} + \text{GR}_T - \text{GR}_c} - \frac{k_{\text{GR,deg}} \cdot \text{GR}_c^*}{K_{\text{GR,deg}} + \text{GR}_c^*} - k_{\text{b,GR}} \cdot F_{\text{per,c}} \cdot \text{GR}_c^* + k_{\text{r,GR}} \cdot \text{FGR(N)}_c \quad (6)$$

$$\frac{d\text{FGR}_c}{dt} = F_{\text{per,c}} \cdot \text{GR}_c - \text{FGR}_c \quad (7)$$

$$\frac{d\text{FGR(N)}_c}{dt} = \text{FGR}_c - \text{FGR(N)}_c \quad (8)$$

Subscript c denotes the level of single peripheral cell. In order to account for the different compartment at the peripheral level, we assumed a transient compartment model (Eq. (2)) [33] using a mean transient time of $\tau = 15$ min [34]. We further assumed that the phosphorylation/dephosphorylation reactions of glucocorticoid and mineralocorticoid receptors (Eqs. (3) and (6)) are governed by Michaelis– Menten kinetics [29]. Finally, in accordance with the theoretical model of [7,13] we assumed a dissociation constant of cortisol for GR ($K_{\text{F,GR}}$) equal to 30 (Eq. (6)) and for MR ($K_{\text{F,MR}}$) equal to 0.5 (Eq. (3)). We further assumed similar reaction kinetics for the two receptors binding and translocation to the nucleus (Eqs. (4), 5,7 and 8). Table 2 provides further information on variable notation.

2.1.2. Peripheral clock genes dynamics

The molecular machinery of peripheral cells that is responsible for circadian time keeping includes a family of genes named *clock genes* which through transcriptional, translational and post-translational feedback loops maintain circadian expression rhythms [35]. Our model incorporates the positive and negative feedback loop among *Per*, *Cry*, *Bmal1* clock genes and CLOCK/BMAL1 heterocomplex. In particular, *Per* and *Cry* genes (Eq. (9)) form a negative feedback module since their proteins (PER/CRY, Eq. (10)), translocate to the nucleus (nuc PER/CRY, Eq. (11)) where they inhibit the CLOCKBMAL1 mediated transcription of their genes (Eq. (1), denominator) while mediating an "accessory" positive feedback loop by indirectly inducing the expression of *Bmal1* gene (Eq. (12)) that its receptor BMAL1 (Eq. (13)) after translocating to the nucleus (nuc BMAL1, Eq. (14)) and forming its active form (CLOCK/BMAL1, Eq. (15)), promotes the transcription of Per/Cry genes (Eq. (1), numerator of first term) [36].

$$\frac{d\text{Per/Cry}_{\text{mRNA,c}}}{dt} = \frac{v_{1b} \cdot (\text{CLOCK/BMAL1}_c + c)}{k_{1b} \cdot \left(1 + \left(\frac{\text{nucPER/CRY}_c}{k_{1i}}\right)^p\right)} - k_{1d} \cdot \text{Per/Cry}_{\text{mRNA,c}} + k_c \cdot \frac{\text{FGR(N)}_c}{\text{CLOCK/BMAL1}_c} \quad (9)$$

$$\frac{d\text{PER/CRY}_c}{dt} = k_{2b} \cdot \text{Per/Cry}_{\text{mRNA,c}}^q - k_{2d} \cdot \text{PER/CRY}_c - k_{2t} \cdot \text{PER/CRY}_c + k_{3t} \cdot \text{nucPER/CRY}_c \quad (10)$$

$$\frac{d\text{nucPER/CRY}_c}{dt} = k_{2t} \cdot \text{PER/CRY}_c - k_{3t} \cdot \text{nucPER/CRY}_c - k_{3d} \cdot \text{nucPER/CRY}_c \quad (11)$$

$$\frac{d\text{Bmal1}_{\text{mRNA,c}}}{dt} = \frac{v_{4b} \cdot \text{nucPER/CRY}_c^r}{k_{4b}^r + \text{nucPER/CRY}_c^r} - k_{4d} \cdot \text{Bmal1}_{\text{mRNA,c}} \quad (12)$$

$$\frac{d\text{BMAL1}_c}{dt} = k_{5b} \cdot \text{Bmal1}_{\text{mRNA,c}} - k_{5d} \cdot \text{BMAL1}_c - k_{5t} \cdot \text{BMAL1}_c + k_{6t} \cdot \text{nucBMAL1}_c \quad (13)$$