MODELLING THE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS RESPONSE TO EXTERNAL PERTURBATIONS WITH CORTISOL

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Abstract
Glucocorticoids, the end products of the Hypothalamic-Pituitary-Adrenal (HPA) axis, are widely used as anti-inflammatory and immunosuppressive drugs. However, the feed-back effects of externally induced glucocorticoids on the HPA axis activity remain widely unknown. In this study, we use numerical simulations to investigate changes in the HPA axis activity caused by externally introduced cortisol. We emulate the basal HPA activity using a stoichiometric model of the HPA axis, and perturb its dynamics by abruptly changing cortisol levels during the course of numerical integration, thereby mimicking cortisol increase under treatment. Our study shows that the HPA axis activity is susceptible to perturbations by cortisol and that external cortisol pulses elicit different responses, depending on the dose and the time of cortisol introduction.

Introduction
The HPA axis is a complex regulatory system that maintains homeostasis under basal physiological conditions and stress. It comprises interactions between key elements of the neuroendocrine system, the hypothalamus, pituitary and adrenal glands [1]. The HPA axis regulates the levels of glucocorticoids, a group of steroid hormones of which cortisol is the most significant representative in humans. Glucocorticoids exert a dual role on the immune system. They are essential for normal immune response functioning, but may also act as potent immunosuppressors [2]. The effect of glucocorticoid therapy on the HPA axis activity is not well understood.

Mathematical modeling and numerical simulations provide a convenient way to investigate how individual components and processes in the HPA axis are integrated to yield a coherent, systemic response. We proposed recently a stoichiometric model to describe the HPA axis activity [3] and validated its predictions under basal conditions and stress [3, 4]. We use here this model to investigate changes in the HPA axis dynamics caused by sudden cortisol increase, thereby mimicking the effect of treatment with glucocorticoids [2].

Results

The HPA model used is described in detail in references [3] and [4]. Numerical simulations were performed using the Matlab program. Single-pulse cortisol perturbations were modeled by abruptly changing the cortisol concentration during the course of the numerical integration.

Cortisol dynamics is governed by complex processes that are characterized by two distinct periods, the ultradian cortisol release occurring every 20-60 minutes (small-amplitude oscillations, Fig. 1) that are superimposed on the 24 h circadian oscillations (large-amplitude oscillations with a 24 h period, Fig. 1) [1, 3, 4]. Single-pulse cortisol perturbations (indicated by arrows in Fig. 1) alter the ultradian cortisol dynamics. Sudden increase in cortisol levels during the night (represented in humans by the ascending phase of the daily cortisol levels, Fig. 1 A) may increase the amplitude of the following ultradian cortisol oscillations, whereas the same perturbation applied during the daytime (represented by the descending phase of the daily cortisol levels, Fig. 1 B) may elicit an opposite response, and decreases the amplitude of the following ultradian oscillation (Fig. 1).

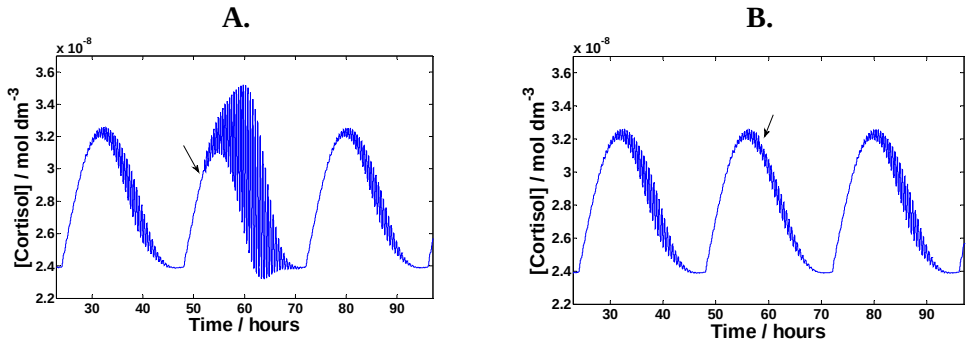

Fig.1. Temporal evolution of cortisol and change in its dynamics after a sudden increase in cortisol levels occurring during the night (**A**) and the daytime (**B**). In both instances, the amount of "added" cortisol is the same, $4 \cdot 10^{-10}$ mol dm^{-3}. The perturbations were applied during the descending phase in arbitrarily chosen ultradian oscillations.

For different cortisol "doses", ranging from $1 \cdot 10^{-11} - 1 \cdot 10^{-9}$ mol dm^{-3}, a complex response of the HPA axis was observed (Fig. 2). Sudden increase in cortisol levels may either decrease or increase the amplitude of the following ultradian oscillations. For example, a decrease in the amplitude of ultradian oscillations was observed during the night phase for cortisol perturbations that were $\leq 1 \cdot 10^{-10}$ mol dm^{-3}, reaching a minimum for perturbations with [cortisol] = $5 \cdot 10^{-11}$ mol dm^{-3}. For perturbations that were $> 1 \cdot 10^{-10}$ mol dm^{-3}, an increase in ultradian cortisol amplitude was observed (Fig. 2, solid rectangles). A similar effect, somewhat less pronounced, was observed for perturbations applied during the daytime (Fig. 2, open rectangles).

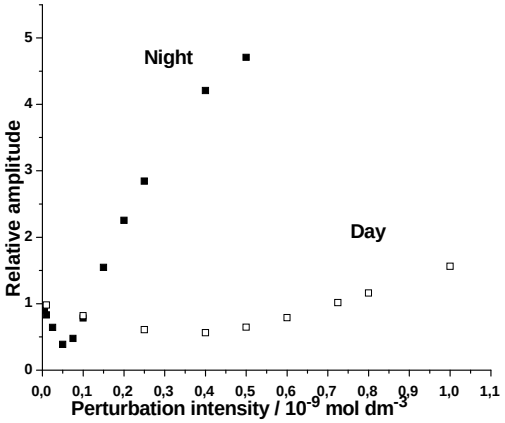

Fig.2. Changes in the amplitude of ultradian cortisol oscillations following a sudden increase in cortisol levels. The intensity of the applied cortisol pulse is given on the abscissa. The relative amplitude is the ratio of the amplitude of a referent ultradian oscillation following cortisol "addition" with respect to the amplitude of the same oscillation prior cortisol ''addition''.

Discussion and Conclusion

Our results show that even very low doses of externally introduced cortisol, which are 1000 times smaller than the basal cortisol concentration, elicit a response and alter the dynamics of the HPA axis. Mathematical modelling emphasized the significance of ultradian and circadian regulation for the HPA axis plasticity, in agreement with increasing number of experimental findings [5,6].

Modeling revealed the intrinsic rhythmicity of the HPA axis and the existence of "sensitive decision points", *i.e.* bifurcation points where the dynamics of the HPA axis changes qualitatively. These phenomena give rise to self-organization and complex dynamic behavior that is not easy to understand intuitively. Realistic models, with good predictive potential enable us to expose the underlying dynamic regulatory mechanisms, predict and explain different responses of the HPA axis to glucocorticoids administration in humans [2].

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