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INFLUENCE OF THE FORM OF THE PERIODIC FUNCTION THAT DESCRIBES THE CIRCADIAN RHYTHM OF THE HPA SYSTEM ACTIVITY

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Abstract

The influence of the form of the periodic function that describes the circadian rhythm on the hypothalamic-pituitary-adrenal (HPA) system self-regulatory activity in humans is discussed. It was found that the HPA system is very sensitive to the choice of this function since it moderates the concentration of all species that are included in the model, as well as the form of ultradian pulses.

Introduction

We have proposed recently [1], [2] an initial model of the hypothalamic-pituitary-adrenal (HPA) system self-regulatory activity in humans. This model is here additionally elaborated in respect to the HPA system activity under stress conditions, with particular attention on the influence of the periodic function that was chosen to describe the daily rhythm.

The proposed model presents simplified picture of complex mechanism of the HPA system activity, with four crucial variables included in it. The species selected for the model are corticotrophin-releasing hormone (CRH), adrenocorticotropin (ACTH), mineralocorticoid aldosterone (M) and glucocorticoid cortisol (G). Analyzing experimental investigations of the mechanism of the HPA system activity, one can conclude that the model ought to take into account the positive feedback effect of cortisol exerted at the level of hippocampal glucocorticoid receptors (GR), where cortisol stimulates CRH gene expression, thus stimulating ACTH and its own production, besides its well known, classical, negative feedback effects at the level of hippocampal mineralocorticoid receptors (MR), and hypothalamic and pituitary GR, and, also, the influence of aldosterone on these feedforward and feedback pathways. Hence, denoting by B, A, G and M the species CRH, ACTH, cortisol and aldosterone, respectively, and by P_1 and P_2 the products of ACTH and cortisol elimination, the proposed model has the form

$$\xrightarrow{k_0} \mathrm{B} \quad \text{(R1)}$$
$$\xrightarrow{k_m} \mathrm{M} \quad \text{(R2)}$$
$$\mathrm{B} \xrightarrow{k_1} \mathrm{A} \quad \text{(R3)}$$
$$\mathrm{A} \xrightarrow{k_2} \mathrm{G} \quad \text{(R4)}$$
$$\mathrm{A} \xrightarrow{k_3} \mathrm{M} \quad \text{(R5)}$$
$$\mathrm{A} + 2\mathrm{G} \xrightarrow{k_4} 3\mathrm{G} \quad \text{(R6)}$$
$$\mathrm{M} + 2\mathrm{G} \xrightarrow{k_5} \mathrm{G} \quad \text{(R7)}$$
$$\mathrm{A} \xrightarrow{k_6} \mathrm{P}_1 \quad \text{(R8)}$$
$$\mathrm{G} \xrightarrow{k_7} \mathrm{P}_2 \quad \text{(R9)}$$

$$\begin{aligned} \frac{db}{d\tau} &= K_0 - b \\ \frac{dm}{d\tau} &= K_m + \alpha\, a - \varphi\, m\, g^2 \\ \frac{da}{d\tau} &= b - (\alpha + \beta + \gamma)\, a - a\, g^2 \\ \frac{dg}{d\tau} &= \beta\, a + a\, g^2 - \varphi\, m\, g^2 - \delta\, g \end{aligned} \quad (1)$$

The first equation describes basal CRH production, the second one describes aldosterone production under the renin-angiotensin system control, the third describes CRH stimulated ACTH production from the pituitary, and the following two are simplified descriptions of the ACTH stimulated cortisol and aldosterone production from adrenal cortex. The sixth equation describes positive feedback of the cortisol, and the next equation represents cortisol negative feedback, acting through hippocampal MR (where aldosterone and cortisol "fight for" the same receptors), as well as hypothalamic and pituitary GR. Cortisol, as represent of the HPA system activity, has double periodic evolution [3]: daily rhythm (of 24 h period), dictated by the internal biological clock (part of the hypothalamus, called the suprachiasmatic nucleus (SCN)), and the other one is the intrinsic hormone oscillatory evolution, with the period of 20-30 minutes (ultradian rhythm). The amplitudes of ultradian oscillations depend on the daily rhythm. They are lower during the night. The HPA system stress reaction depends of both functions: f(*intrinsic*) and f(*daily*). We shall discuss only the influence of the mathematical form of the function that describes daily rhythm on the HPA system response to an acute stressor. This function can be simple sinusoidal function, or combination of sinusoidal one and others that help in obtaining the asymmetric form of a period that is more closed to the human being daily rhythm. Such function can also be the one proposed in our previous paper [2] given as P = 0.8095 + 0.061248×sin(2πt/1440) + 0.11484×abs(sin(πt/1440)) (where the constant 1440 is expressed in minutes) or any similar [2]. In that case, the rate of inflow of CRH into the system is changed, such that new rate of inflow is $K_P = K_0 \times P$.

Results and Discussion

The sensitivity of the model to the selection of the function that describes daily rhythm is analyzed for different functions. In Figure 1, we can see two very similar basal functions (A) and (B) and one sinusoidal (C). Perturbations were performed during the day, in downward inflection point of one cortisol pulse.

Conclusion

Numerical simulations performed, for two different functions chosen to describe daily rhythm of the HPA system, show that the form of these functions clearly influences the systems response to stressful stimuli. This is in accordance with known fact that the same stressful situation can cause different stress responses in different subjects. Between humans significant differences in daily rhythm of the HPA system exist, whilst it is quite stabile for one person during life.

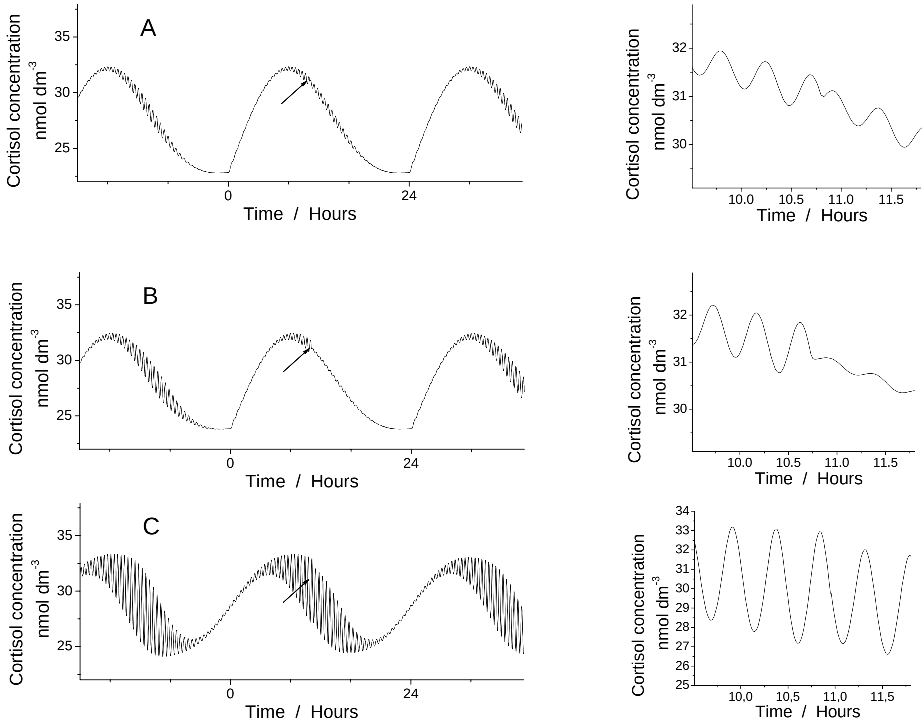

Fig. 1. Perturbations of the HPA system with two different functions of daily rhythm. The augmented segments, where perturbations in CRH concentration equal to 1×10^{-9} moldm^{-3} was performed, are presented on the right side: $G(0) = 2.76 \times 10^{-8}$ moldm^{-3}; $K_0 = 0.0831$; $K_m = 2.7693 \times 10^{-4}$; $\alpha = 1.5776 \times 10^{-4}$; $\beta = 0.0197$; $\gamma = 0.0293$; $\delta = 0.2245$; $\varphi = 0.0560$; (A) $P = 0.7904 + 0.0689 \times \sin(2\pi t/1440) + 0.1292 \times \mathrm{abs}[\sin(\pi t/1440)]$; (B) $P = 0.8095 + 0.0612 \times \sin(2\pi t/1440) + 0.1148 \times \mathrm{abs}[\sin(\pi t/1440)]$; (C) $P = 0.8980 + 0.0640 \times \sin(2\pi t/1440)$

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