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A mathematical model of the hypothalamo-pituitary-adrenocortical system and its stability analysis

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Abstract

It is commonly assumed that the hypothalamo-pituitary-adrenocortical (HPA) axis generates oscillations, because a regular daily rhythm of its component hormones is observed. We offer another plausible explanation of the origin of its circadian oscillations: HPA just responds to an independent external pacemaker (from the suprachiazmatic nucleus, SCN). Five versions (with and without time delay) of a qualitative non-phenomenological mathematical model of the HPA axis as a feedback mechanism are constructed wherein all the terms in the equations are introduced according to the rules of chemical kinetics, i.e. are physicochemically interpretable. The dynamics of the HPA axis model was examined using linear stability analysis. The results show stability of this system, meaning that it does not generate diurnal oscillations. Computer simulation based on this model shows oscillations that are system's response to an external pulsing activator (SCN) implying that the observed time-periodic pattern does not have to be an intrinsic property of the HPA axis.

1. Introduction

Most physiological systems in an organism have regular daily—circadian (diurnal)—rhythms of functioning that is essential for the organism. Suprachiazmatic nucleus (SCN) of the hypothalamus is known to be the master component of the circadian timing system. It contains a set of the so-called clock genes that are expressed periodically. Clock genes exist in most of the other tissues, but their expression is synchronized by those in the SCN that adjust to environmental factors, main of which is light (the contribution of the non-photic stimuli is small [1]). A partial redundancy of function among some subsets of clock gene products confirms the importance of rhythmicity [2].

Hypothalamo-pituitary-adrenocortical (HPA) axis is one of the most important systems in stress response (along with the sympathetic nervous system). Roughly, its role in stress conditions is to "alarm" the organism and to quickly direct energy to brain and muscles, so that a person (or an animal) can react in a stressful situation. In a healthy organism, the HPA axis is adjusted to react immediately in stress conditions and to return to basal level within hours.

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Although mostly mentioned for their role in stress, glucocorticoids (mainly cortisol in humans)—the final product of the HPA axis—are one of the major physiological regulators and they affect almost all mammalian tissues (for description of their numerous roles see, for example, [3]). It seems that one of their functions is to convey rhythmic signals from SCN and thus synchronize bodily systems with environmental changes [4]. This makes HPA axis one of the main links between the master pacemaker and peripheral oscillators. If this function were disturbed, the synchronization of many vital processes would be disrupted and the effects could even be lethal. That is why the stability of the HPA axis dynamics is so important.

HPA axis consists of two CNS structures—hypothalamus and pituitary—and adrenal cortex. Paraventricular nuclei (PVN) of the hypothalamus generate corticotropin releasing hormone (CRH) which induces the adenocorticotropin (ACTH) production in the pituitary; subsequently, ACTH stimulates the adrenal cortex to produce glucocorticoids, which in turn suppress the production of both CRH and ACTH, the first suppression considered to be more important (Fig. 1) (for example, [5]). Many other structures influence the HPA axis system [5–16], but these three hormones form its "backbone".

In general, a reaction system with a negative feedback loop is capable of generating oscillations [17,18]. Our goal is to mathematically examine whether time periodicity observed in cortisol dynamics is the result of: (1) the system's response to the independent external pacemaker solely or (2) a superposition of HPA's intrinsic oscillations and the periodic pulsatile stimulus from SCN. In the latter case, there would exist a possibility of generating quite complicated time-patterns. Multiple periodic, quasi-periodic or even chaotic dynamics could emerge.

1.1. Mathematical models of HPA

Not many mathematical models of the HPA system dynamics exist. Except for the models of Gonzalez-Heydrich et al. [19] and Lenbury and Pacheenburawana [20], all the others describe only the cortisol dynamics (the influence of other hormones is taken into account through model parameters). Statistical [21–24], dynamical [25], or combined [26,27], they all have one main goal: to make the best possible fitting curves to clinical data. As the majority of these studies is done for pharmacological and therapeutic purposes mainly, the aim of quantitatively predicting the level of cortisol after administration of a medicament is fulfilled by these methods.

Most of these models use simple trigonometric functions or their combinations to produce oscillations, which is a legitimate phenomenological approach. One of the shortcomings of phenomenological models is that they do not explain the origin of observed behavior. Dokoumetzidis and his collaborators [25] justly stressed the importance of the feedback mechanism, but the cosine function they introduced as the source of oscillations and the nth power of this term are not explained. Numerical solution of this model shows chaotic behavior of cortisol secretion.

Londergan and Peacock-Lopez [28] also obtain chaos numerically in a general feedback based model. They suggest that their model of two coupled oscillators could be applied to interaction between the hypothalamus and the pituitary gland. The coupling of (inhibition) functions between the two oscillators is again phenomenological. Ilias et al. [29] attain chaotic cortisol behavior from a constructed 10-days time series from data on 24-h cortisol secretion of ten individuals assuming that all subjects have a similar diurnal pattern. Even though they calculate the fractal dimension of the attractor, they are cautious in the interpretation of their results because of the sample limitations (small number of subjects, short time period).

The model of Lenbury and Pacheenburawana [20] deserves special attention because, to our knowledge, it is the only model beside ours that has analytical examination of stability. The main difference is that their model has a cosine function (representing a periodic nervous system stimulation) that classifies it in the category mentioned above. This term renders intrinsic oscillations and chaotic solution for a range of parameters in their model.

There is not enough evidence for chaotic behavior of cortisol secretion. To quote Berry [30]: "... univocal proofs of chaotic behaviors in real biological systems are still missing. Despite this uncertainty, chaotic dynamics are attractive to biologists, because they could provide biological systems with a wide richness of behaviors to explain biological oscillations and rhythms...". We do not want to step in the "trap" of attractiveness. Of course, deterministic chaotic behavior exists in biological systems, but our opinion is that in the case of cortisol those models should wait. Diurnal

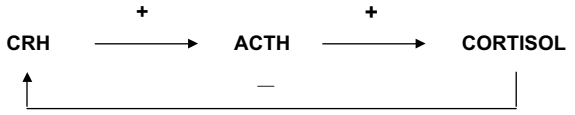

Fig. 1. A simple schematic representation of the HPA axis reaction chain with the negative feedback. The plus signs denote activation, minus sign denotes inhibition (suppression).

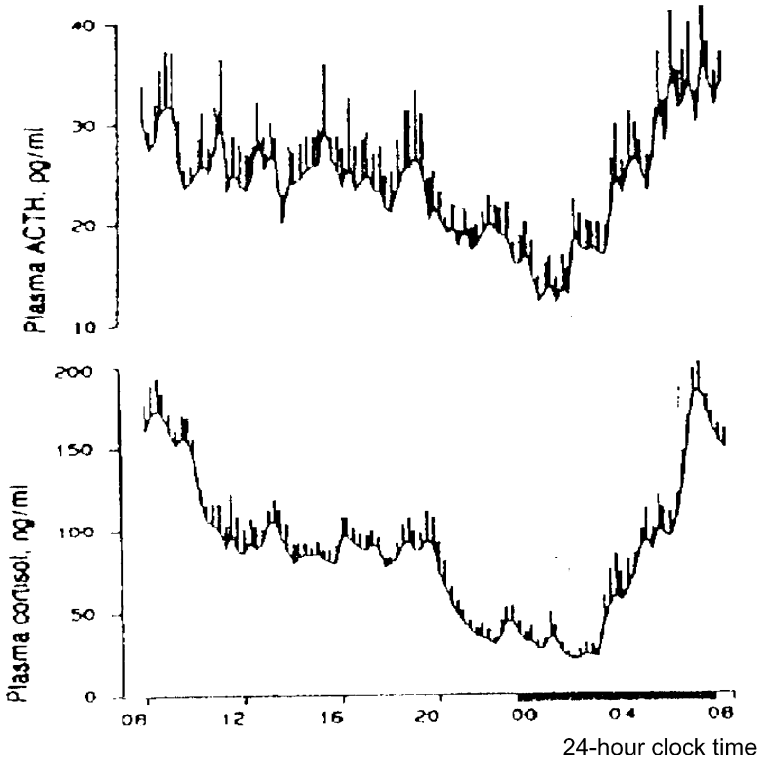

Fig. 2. Diurnal secretion of plasma ACTH and cortisol: a regular periodic function with one minimum—at night—and one maximum—in the morning. (The drawing is taken from [35].)

one-maximum–one-minimum pattern is recognized in all clinical measurements (Fig. 2) and is even preserved in most of the stress-induced disorders thus deserving to be modeled.

1.2. Does HPA axis have intrinsic oscillations or not?

Our aim is to examine whether time periodicity can emerge in the model of HPA axis system without introducing the "ready to use" best-fitting trigonometric function. Here we present five versions of a qualitative mathematical model of the HPA axis activity based on a negative feedback mechanism, created according to the rules of chemical kinetics with each term being physicochemically interpretable. The empirically justified modifications are gradually introduced into the model in trials to obtain intrinsic oscillations. This stepwise fashion of elaborating the model provides a good learning example of how a model is made.

Then we analyze stability of each of the models using methods of linear stability analysis. It enables examination of qualitative types of behavior and the conditions for its changes (bifurcations).

Systems of nonlinear differential equations are still difficult to solve. Nevertheless, mathematical tools of stability theory are sufficient for analyzing general character of such processes. In terms of stability theory, the solution rendering oscillating motion is a *limit cycle*—a closed trajectory (orbit) in phase space along which the system undergoes sustained oscillations.

2. Results

2.1. Model 1

A standard way in chemical kinetics to model a cascade of reactions shown in Fig. 1 is

$$\frac{\mathrm{dCRH}}{\mathrm{d}t} = k_1 \cdot \left(1 - \eta \cdot \frac{\mathrm{CORT}}{K_\mathrm{d} + \mathrm{CORT}}\right) - k_2 \cdot \mathrm{CRH} \tag{1.1}$$

$$\frac{\mathrm{dACTH}}{\mathrm{d}t} = k_2 \cdot \mathrm{CRH} - k_3 \cdot \mathrm{ACTH} \tag{1.2}$$

$$\frac{\mathrm{dCORT}}{\mathrm{d}t} = k_3 \cdot \mathrm{ACTH} - k_4 \cdot \mathrm{CORT} \tag{1.3}$$

where all the first terms on the right represent production and all the second terms represent spending of hormones. CRH, ACTH, and CORT are the concentrations of stress hormones; k_1, k_2, k_3, and k_4 are the reaction rate constants; K_d is the dissociation constant of the cortisol-receptor complex (CRC); η is a constant whose meaning will be explained below. It is taken, as the first approximation, that CRH and ACTH are spent solely on producing ACTH and cortisol, respectively. The most important regulatory loop includes formation of CRC which stops the hypersecretion of CRH. This regulating function is represented by the term $\eta \cdot \mathrm{CORT}/(K_\mathrm{d} + \mathrm{CORT})$ of the Michaelis-Menten form (derived from mass action law, Appendix A) in Eq. (1.1). It is reasonable to assume that the interaction of cortisol and its receptor is faster than the other reactions in the system, so we take it to be in equilibrium on the observed time scale. When $\mathrm{CORT} \gg K_\mathrm{d}$, this function approaches saturation, i.e. the majority of receptors is occupied and further secretion of cortisol does not influence the CRH production. When the number of CRC molecules approaches R_tot (total number of receptors), k_1 is decreased for a maximal fraction η—the suppression is maximal. So, η is a constant between 0 and 1, directly depending on R_tot.

Simplifications of this model are that (a) only one (the main) inhibition—acting on CRH production—was taken into account and (b) an assumption that total CRH and ACTH are spent exclusively on inducing the next hormone in the chain: ACTH and cortisol, respectively.

In our previous work [31], these three equations were a part of a more complex model of stress response to psychological stressors with accents on individual differences in such conditions. The only shifts in concentrations that were of interest were the ones induced by a stressor, so the diurnal variations of hormone concentrations were not taken into account. Such an approach was justified by the fact that concentration changes caused by stress highly exceed daily fluctuations. The incapacity of Model 1 to generate oscillations, that was observed in computer simulations, was confirmed by linear stability analysis [32] showing that Model 1 has an asymptotically stable single point solution S_0 (CRH_0, ACTH_0, CORT_0; where index "0" denotes steady state concentrations of hormones, obtained by using the condition that net reaction rates are zero). Limit cycle usually appears through a supercritical Hopf bifurcation of a stationary state [33]. The stable stationary state becomes unstable and an attracting (stable) limit cycle is born. Thus, a way to obtain self-organized oscillatory dynamics is the existence of a Hopf bifurcation. Model 1 does not fulfill the needed conditions.

2.2. Model 2

A delay in dynamics of at least one of the components often has a destabilizing effect and can cause the appearance of oscillatory solutions [34,17]. We introduce a delay in cortisol production. As can be seen in Fig. 2, although small, the delay exists [35], because ACTH has a long way from pituitary to adrenal cortex via portal blood circulation. The other two possible delays are neglected being even smaller: delay in cortisol regulation of CRH production—because steroid molecules (cortisol) are small and diffuse quickly, and, delay in ACTH production—because the distance between hypothalamus and pituitary is significantly shorter than the distance between pituitary and adrenal cortex.

Now the Model 2 has the form

$$\frac{\mathrm{dCRH}}{\mathrm{d}t} = k_1 \cdot \left(1 - \eta \cdot \frac{\mathrm{CORT}}{K_\mathrm{d} + \mathrm{CORT}}\right) - k_2 \cdot \mathrm{CRH} \tag{2.1}$$

$$\frac{\mathrm{dACTH}}{\mathrm{d}t} = k_2 \cdot \mathrm{CRH} - k_3 \cdot \mathrm{ACTH} \tag{2.2}$$

$$\frac{\mathrm{dCORT}}{\mathrm{d}t} = k_3 \cdot \mathrm{ACTH}(t-\tau) - k_4 \cdot \mathrm{CORT} \tag{2.3}$$

where τ is time delay in ACTH-induced cortisol production. In other words, τ is a time interval needed for ACTH molecules to reach adrenal cortex from the pituitary gland: at a given moment t, cortisol production depends on the amount of ACTH that was produced τ time units earlier.

First, we find steady state concentrations CRH_0, ACTH_0, and CORT_0, bearing in mind that $\mathrm{ACTH}(t-\tau)_0 = \mathrm{ACTH}_0$. Then, we assume that fluctuations follow the same dynamics given by Eqs. (2.1)–(2.3). The assumption that they are small allows us to linearize the equations around the steady state S_0 and seek solutions in

the form of normal modes: $\delta\mathrm{CRH}(t)$, $\delta\mathrm{ACTH}(t)$, and $\delta\mathrm{CORT}(t) \sim \exp(\lambda t)$, $\delta\mathrm{ACTH}(t-\tau) \sim \exp(\lambda t)\cdot\exp(-\lambda\tau)$, δ denoting fluctuations, λ is the eigen value of the linearizing operator. We obtain the so-called characteristic equation

$$\lambda^3 + A\lambda^2 + B\lambda + C + D\exp(-\lambda\tau) = 0 \tag{2.4}$$

with $A = k_2 + k_3 + k_4$, $B = k_2k_3 + k_3k_4 + k_2k_4$, $C = k_2k_3k_4$, and $D = k_1k_2k_3\eta K_\mathrm{d}/(K_\mathrm{d} + \mathrm{CORT}_0)^2$.

Limit cycle is the result of bifurcation for parameters giving purely imaginary roots of (2.4): $\mathrm{Re}\,\lambda = 0$, $\mathrm{Im}\,\lambda = \pm\omega$.

Supposing that such roots exist, after some simple transformations, we get

$$\omega^6 + M\omega^4 + N\omega^2 + R = 0 \tag{2.5}$$

where $M = A^2 - 2B$, $N = B^2 - 2AC$, and $R = C^2 - D^2$. After expressing M, N, and R through system parameters, it can be shown that they are all positive. Hence, there are no real solutions for ω and consequently, no limit cycle. Again, Eq. (2.4) has only one solution which is real and negative, meaning that the steady state is stable.

Thus, Model 2 also does not generate oscillations.

2.3. Model 3

Increasing the complexity of a qualitative mathematical model is justified only when simpler forms cannot simulate the observed phenomena. Next step was to introduce delays into production terms of all three hormones (even though the first two are much smaller) and apply six rate constants (as they really exist) instead of three:

$$\frac{\mathrm{dCRH}}{\mathrm{d}t} = k_1 \cdot \left[1 - \eta \cdot \frac{\mathrm{CORT}(t-\tau_1)}{K_\mathrm{d} + \mathrm{CORT}(t-\tau_1)}\right] - k_2 \cdot \mathrm{CRH} \tag{3.1}$$

$$\frac{\mathrm{dACTH}}{\mathrm{d}t} = k_3 \cdot \mathrm{CRH}(t-\tau_2) - k_4 \cdot \mathrm{ACTH} \tag{3.2}$$

$$\frac{\mathrm{dCORT}}{\mathrm{d}t} = k_5 \cdot \mathrm{ACTH}(t-\tau_3) - k_6 \cdot \mathrm{CORT} \tag{3.3}$$

Even these interventions do not qualitatively change the characteristic equation:

$$\lambda^3 + A\lambda^2 + B\lambda + C + D\exp(-\lambda(\tau_1 + \tau_2 + \tau_3)) = 0 \tag{3.4}$$

with all the constants: $A = k_2 + k_4 + k_6$, $B = k_2k_4 + k_2k_6 + k_4k_6$, $C = k_2k_4k_6$, and $D = k_1k_3k_5\eta K_\mathrm{d}/(K_\mathrm{d} + \mathrm{CORT}_0)^2$ being positive (obtained by the same procedure as above) and consequently an equation analogous to (2.5) applies.

2.4. Model 4

Let us remember the common approximation we made in Model 1: knowing that the main self-regulation (negative feedback loop) of the HPA axis acts on CRH production, we neglected the direct inhibition of ACTH secretion by cortisol. Following the same line of reasoning—making the model more complex until we obtain the realistic picture—we introduce an analogous regulation term in the second equation:

$$\frac{\mathrm{dCRH}}{\mathrm{d}t} = k_1 \cdot \left(1 - \eta \cdot \frac{\mathrm{CORT}}{K_\mathrm{d} + \mathrm{CORT}}\right) - k_2 \cdot \mathrm{CRH} \tag{4.1}$$

$$\frac{\mathrm{dACTH}}{\mathrm{d}t} = k_3 \cdot \left(1 - \mu \cdot \frac{\mathrm{CORT}}{K_\mathrm{d} + \mathrm{CORT}}\right) \cdot \mathrm{CRH} - k_4 \cdot \mathrm{ACTH} \tag{4.2}$$

$$\frac{\mathrm{dCORT}}{\mathrm{d}t} = k_5 \cdot \mathrm{ACTH} - k_6 \cdot \mathrm{CORT} \tag{4.3}$$

where μ depends on the concentration of cortisol receptors in the pituitary. K_d is the same because the affinity of cortisol to its receptors does not change with reaction site.

For simplicity, the system was made dimensionless [17]:

$$\frac{\mathrm{d}X}{\mathrm{d}\theta} = 1 - \eta \cdot \frac{Z}{1+Z} - \alpha \cdot X \tag{4.1a}$$

$$\frac{dY}{d\theta} = \left(1 - \mu \cdot \frac{Z}{1+Z}\right) \cdot X - \beta \cdot Y \tag{4.2a}$$

$$\frac{dZ}{d\theta} = Y - \gamma \cdot Z \tag{4.3a}$$

where $\theta = C_0 t$; $\mathrm{CRH}(t) = X(\theta)C_1$, $\mathrm{ACTH}(t) = C_2 Y(\theta)$, and $\mathrm{CORT}(t) = C_3 Z(\theta)$; C_0, C_1, C_2, and C_3 are positive proportionality constants (combinations of reaction rate constants).

Characteristic equation has the same form as (3.4), but without the fourth term.

$$\lambda^3 + A\lambda^2 + B\lambda + C = 0 \tag{4.4}$$

Coefficients now read: $A = \alpha + \beta + \gamma$, $B = Z_0\beta\ \gamma/(1 + Z_0) + \alpha(\beta + \gamma) + (1 + Z_0(1 - \eta))/\alpha Z_0\ (1 + Z_0)^2$, $C = (1 + (Z_0 - 1)Z_0\alpha\beta\gamma)/Z_0(1 + Z_0) + \alpha\beta\ \gamma/(1 + Z_0(1 - \eta)) - \eta/(1 + Z_0)^2$ and are again positive (so, if any λ's are real, they must be negative).

A is minus trace of the matrix (M) of the linearized system (4) around the stationary state ($A = -\operatorname{tr} M$); B is the sum of partial second order determinants; and C is minus determinant of the matrix ($C = -\det M$). The condition for a Hopf bifurcation leading to a limit cycle is: $AB - C = 0$, $A > 0$ [36].

After some algebraic transformations, we get

$$AB - C = \alpha^2(\beta + \gamma) + \frac{\beta\gamma(\beta + \gamma)Z_0}{1 + Z_0} + \alpha\left(\beta^2 + \gamma^2 + \beta\gamma \cdot \frac{2 + Z_0(4 - 3\eta) + 2Z_0^2(1 - \eta)}{(1 + Z_0)(1 + Z_0(1 - \eta))}\right) + \frac{(\beta + \gamma)(1 + Z_0(1 - \eta))}{Z_0(1 + Z_0)^2\alpha} \succ 0$$

where $\alpha = \frac{k_2 K_d}{k_5}$, $\beta = k_4\left(\frac{K_d}{k_1 k_3 k_5}\right)^{1/3}$, $\gamma = k_6\left(\frac{K_d}{k_1 k_3 k_5}\right)^{1/3}$.

As all the elements are positive (let us remember that $\eta < 1$), we proved that $AB - C > 0$. Again, there are no oscillatory solutions.

2.5. Model 5

Finally, we introduce time delay into Model 4

$$\frac{d\mathrm{CRH}}{dt} = k_1 \cdot \left(1 - \eta \cdot \frac{\mathrm{CORT}}{K_d + \mathrm{CORT}}\right) - k_2 \cdot \mathrm{CRH} \tag{5.1}$$

$$\frac{d\mathrm{ACTH}}{dt} = k_3 \cdot \left(1 - \mu \cdot \frac{\mathrm{CORT}}{K_d + \mathrm{CORT}}\right) \cdot \mathrm{CRH} - k_4 \cdot \mathrm{ACTH} \tag{5.2}$$

$$\frac{d\mathrm{CORT}}{dt} = k_5 \cdot \mathrm{ACTH}(t - \tau) - k_6 \cdot \mathrm{CORT} \tag{5.3}$$

Again, as above, we use the dimensionless form

$$\frac{dX}{d\theta} = 1 - \eta \cdot \frac{Z}{1+Z} - \alpha \cdot X \tag{5.1a}$$

$$\frac{dY}{d\theta} = \left(1 - \mu \cdot \frac{Z}{1+Z}\right) \cdot X - \beta \cdot Y \tag{5.2a}$$

$$\frac{dZ}{d\theta} = Y(\theta - \tau) - \gamma \cdot Z \tag{5.3a}$$

The only difference from Model 4 is in the term $Y(\theta - \tau) = Y(\theta)\exp(-\lambda\tau)$. We apply the same method, but the procedure is longer than in the previous cases, so it is given in Appendix B. It is shown there that Model 5 does not render limit cycle.

To resume: Models 1–5 are all based on a negative feedback mechanism with cortisol regulating the production of HPA axis hormones. Taking into account one (Models 1–3) or two (Models 4 and 5) inhibition terms, and time delays of hormone production (Models 2, 4 and 5) did not result in intrinsic oscillations.

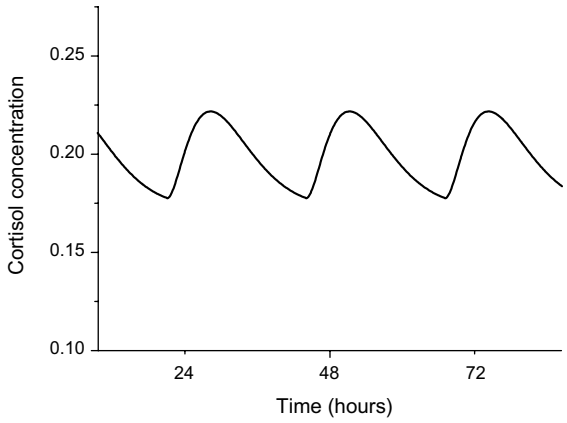

Fig. 3. Computational simulation of the HPA axis system obtained by numerical solution of the Model 1 with time-periodic activators (ultradian and circadian) of CRH production (Eq. (1.1a)).

2.6. A pulsing activator

Hypothalamic PVN cells produce CRH and pack it in vesicles wherefrom it is released into the system in bursts with the frequency of 1–3 times per hour [37] forming the ultradian rhythm. The other two major HPA hormones have similar ultradian fashion of secretion. A diurnal one-maximum pattern is due to one large stimulus from the SCN per day. This stimulus superimposes ultradian secretion, giving rise to a larger burst of CRH. The interplay of production and spending of all three hormones together with the cortisol suppression just smoothes the curve. Hence, a simple increase in CRH production once a day is enough to explain what we see. Provided a periodic stimulus from SCN, even the simplest form of our model (Model 1) allows smooth time-periodic pattern (Fig. 3).

With introducing a circadian activator S into the Model 1, Eq. (1.1) becomes

$$\frac{\mathrm{dCRH}}{\mathrm{d}t} = S \cdot k_1 \cdot \left(1 - \eta \cdot \frac{\mathrm{CORT}}{K_\mathrm{d} + \mathrm{CORT}}\right) - k_2 \cdot \mathrm{CRH} \tag{1.1a}$$

where $S > 1$ is applied for iteration numbers that are multiples of I_S, i.e. $I = j \cdot I_S$ ($j = 1, \ldots, n_S$) and $S = 1$ for $I \neq j \cdot I_S$. The rate constant of CRH production, k_1, is mimicking the ultradian pulsing: $k_1 > 0$ for $I = m \cdot I_k$ ($m = 1, \ldots, n_k$), and $k_1 = 0$ for $I \neq I_k$. The ratio of circadian/ultradian rhythmicity is kept realistic by applying the frequencies ratio $I_S/I_k = 1/24$ (circadian stimulus acts once a day and ultradian bursts occur hourly); the other equation parameters are chosen arbitrarily.

3. Discussion and concluding remarks

According to our results obtained by stability analysis of our model(s), HPA axis is asymptotically stable, which might seem counterintuitive at first sight. *As a system*, it does not oscillate at all (the ultradian pulsing of hormones is not a system's characteristic, but an intrinsic property of each component separately)—the observed function of hormone concentration vs. time is exclusively the consequence of responding to a time-periodic signal (from SCN).

If the HPA axis system were the generator of oscillations, i.e. if we had a case of limit cycle, the response of the HPA axis to the pulsatile release of CRH could be qualitatively different from the usually observed one. Pulsatile periodic perturbations of a limit cycle oscillator could result in a sequence of bifurcations, as the parameters are varied, leading to multi-dimensional oscillations and eventually to chaotic dynamics.

The empirical data available is not sufficient to suggest that any of these more complicated dynamic patterns are the basis of the observed daily variations of the cortisol. The smaller scale peaks superimposed on the daily pattern of cortisol secretion (Fig. 2) do not indicate chaos. They reflect the activity of internal ultradian pacemakers and probably stochastic influence of many neurohormones and transmitters that are known to modulate HPA axis functioning.

It is worth mentioning that SCN is one of the very few structures without glucocorticoid receptors [4]. This means that its relation with the HPA is one-way, excluding the SCN from inhibitory (or any other) action of cortisol and thus making circadian rhythmicity protected from stress perturbations. The fact that circadian frequency is maintained in

the majority of stress-induced disorders (although the hormone amplitude can be increased) confirms the significance of preserving circadian rhythmicity. In this light, our model that is asymptotically stable makes a lot of sense.

Acknowledgements

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Appendix A

The inhibition term $\eta \cdot \frac{\mathrm{CORT}}{K_\mathrm{d}+\mathrm{CORT}}$ in the CRH production is derived from the equilibrium reaction of cortisol and its receptor forming a complex

$$\mathrm{CORT} + R \underset{k_\mathrm{d}}{\overset{k_\mathrm{a}}{\Longleftrightarrow}} \mathrm{CRC}$$

In equilibrium, mass action law gives

$$k_\mathrm{a}[\mathrm{CORT}] \cdot [R] = k_\mathrm{d}[\mathrm{CRC}] \Rightarrow K_\mathrm{d} = [\mathrm{CORT}] \cdot [R]/[\mathrm{CRC}]$$

where $K_\mathrm{d} = k_\mathrm{d}/k_\mathrm{a}$ is the dissociation constant of CRC.

Expressing the concentration of the free receptor (R) as the difference between the concentrations of total and bound (in the complex with cortisol) receptors

$$R = R_\mathrm{tot} - \mathrm{CRC}$$

we get

$$\mathrm{CORT} \cdot (R_\mathrm{tot} - \mathrm{CRC}) = K_\mathrm{d} \cdot \mathrm{CRC} \Rightarrow \mathrm{CRC} = R_\mathrm{tot} \cdot \frac{\mathrm{CORT}}{K_\mathrm{d} + \mathrm{CORT}}$$

The inhibition of CRH production depends on CRC, so the final form of the inhibition term becomes

$$\eta \cdot \frac{\mathrm{CORT}}{K_\mathrm{d} + \mathrm{CORT}}$$

where $\eta = \mathrm{const} \cdot R_\mathrm{tot}$ is a constant between 0 and 1.

Appendix B

The matrix of the system (5.1a), (5.2a), (5.3a) reads

$$\begin{pmatrix} -\alpha-\lambda & 0 & -p \\ q & -\beta-\lambda & -r \\ 0 & \mathrm{e}^{-\lambda\tau} & -\gamma-\lambda \end{pmatrix}$$

where $p = \frac{\eta}{(1+Z_0)^2}$, $q = 1 - \frac{\mu Z_0}{1+Z_0}$, and $r = \frac{\mu X_0}{(1+Z_0)^2}$ (α, β and γ are the same as in Model 4).

We can write the characteristic equation in the following form:

$$\lambda^3 + (\alpha+\beta+\gamma)\lambda^2 + (\alpha\beta+\alpha\gamma+\beta\gamma)\lambda + \alpha\beta\gamma + [(\lambda+\alpha)\cdot r + pq]\exp(-\lambda\tau) = 0 \tag{5.4}$$

Again, we search the purely imaginary roots of (5.4). We then insert $\mathrm{i}\omega$ instead of λ, and write $\exp(-\lambda\tau)$ as $\cos(\omega\tau) - \mathrm{i}\sin(\omega\tau)$. Equating the real part and the imaginary part with zero from Eq. (5.4), we get:

$$\begin{aligned} &-(\alpha+\beta+\gamma)\omega^2 + \alpha\beta\gamma + (\alpha r + pq)\cdot\cos(\omega\tau) + r\omega\cdot\sin(\omega\tau) = 0 \\ &\omega^3 - (\alpha\beta+\alpha\gamma+\beta\gamma)\omega + (\alpha r + pq)\cdot\sin(\omega\tau) - r\omega\cdot\cos(\omega\tau) = 0 \end{aligned} \tag{5.5}$$

Rearranging (5.5) to express $\sin(\omega\tau)$ and $\cos(\omega\tau)$ and knowing that $\sin^2(\omega\tau) + \cos^2(\omega\tau) = 1$, we obtain

$$\frac{(\omega^2+\alpha^2)(\omega^2+\beta^2)(\omega^2+\gamma^2)}{r^2\omega^2 + (\alpha r + pq)^2} = 1 \tag{5.6}$$

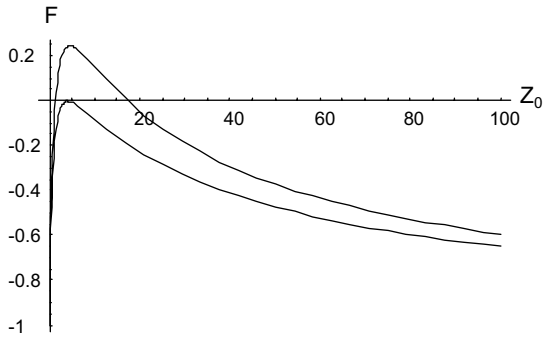

Fig. 4. Dependence of F on Z_0 for $\eta = 0.98$ and: $\mu = 0.90$ (upper curve) and $\mu = 0.72$ (lower curve).

We can analyze (5.6) as the intersection of the two functions

$$(\omega^2 + \alpha^2)(\omega^2 + \beta^2)(\omega^2 + \gamma^2) = r^2\omega^2 + (\alpha r + pq)^2$$

For $\omega \to 0$, we get

$$\begin{aligned} &\alpha\beta\gamma \cong \alpha r + pq \\ &\text{For } (\alpha r + pq) > \alpha\beta\gamma \end{aligned} \tag{5.7}$$

intersection exists, i.e. the oscillations exist. If $(\alpha r + pq) \leqslant \alpha\beta\gamma$, the functions do not intersect and hence there is no limit cycle.

We express the α, β, γ, p, q, and r through η, μ, and the steady state concentration Z_0 of the system (5.1a), (5.2a), (5.3a); then we rearrange them to obtain

$$F = \frac{Z_0(\eta \cdot a + \mu \cdot b)}{(1 + Z_0) \cdot a \cdot b} - 1$$

where $a = 1 + Z_0(1 - \mu)$ and $b = 1 + Z_0(1 - \eta)$.

The condition (5.7) now has the following form:

$$F > 0 \tag{5.7a}$$

We want to estimate the range of Z_0 in which the limit cycle is possible.

Knowing that the inhibition on the level of pituitary is significantly weaker than the one acting on CRH production we write: $\mu < \eta$. Eta usually takes values very near unity. Plotting the function F against Z_0 (Fig. 4) we see that the positive domain of F narrows down as η and μ decrease. Taking $\eta = 0.98$ and $\mu = 0.72$, we get F completely in the negative region. Even for larger μ, the positive domain of F is in the region of Z_0 values that are less than realistic (realistic $Z_0 \in [50,100]$). Z_0 (=CORT/K_d) was estimated from empiric values of average cortisol concentration [3] and K_d (Gonzalez-Heydrich et al., 1994). Hence for realistic values of η, μ and cortisol, there is no limit cycle.

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