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SLOW PERIODIC OSCILLATIONS IN HYPOTHALAMIC–PITUITARY–ADRENAL AXIS

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A structured model of the hypothalamic-pituitary-adrenal (HPA) axis that includes a glucocorticoid receptor (GR) is considered. The model includes nonlinear dynamics of pituitary GR synthesis. The nonlinear effect arises from the fact that GR homodimerizes after cortisol activation and induces its own synthesis in the pituitary. The homodimerization makes possible two stable steady states (the low and the high one) and an unstable state. The model includes also a delay on stress. It is shown that competition between the trajectories of a dynamical system, which are produced by the unstable manifold and the value of delay time τ, results in slow asymptotic periodic oscillations of cortisol with a period, which is greater than 2τ. It is shown that the oscillations exist only in the interval $\tau_1 < \tau < \tau_2$, where exact formulas for τ_1 and τ_2 has been obtained. The oscillations arise when the initial value of stress is larger of some threshold.

Keywords: hypothalamic-pituitary-adrenal axis, asymptotic periodic oscillations, negative feedback, difference-differential delay equations, normal state

Introduction

Hormone regulation is a complex process where the level of a single hormone is tightly related to the levels of the rest. The chain of hormone interactions is a closed one that provides self-regulation of a living organism. Hormone dynamics was an object of a number of mathematical models. Mostly they imply the solution of a system of differential equations with a set of feedbacks involved. They are able to describe general tendencies without detailed agreement of the results and the experimental data. Experimentally registered oscillations of hormone content are usually far from the periodic form and include irregular components. Developed later stochastic and chaotical models have demonstrated better agreement with the experimental testing.

We consider HPA dynamics which includes stored corticotrophin-releasing hormone (CRH), circuiting CRH and adrenocorticotropic hormone (ACTH), cortisol and glucocorticoid receptor that plays a role of «dispatcher» that controls distributions of hormones in the system. Our model incorporates a self-upregulation of CRH release, a negative and positive feedback effect on cortisol in CRH synthesis and a delay in ACTH- activated cortisol synthesis [1]. It is worth reminding

that hypothalamic-pituitary-adrenal (HPA) axis is a neuroendocrine system that regulates hormones. The regulation is mediated by inhibition of peptide hormones such as corticotrophin-releasing hormone and adrenocorticotropic hormone by circulating glucocorticoids such as cortisol (CORT).

Note that in this paper, we do not start with the local linear stability theory, because our experience suggests as cited in [2]: «Many experimentalists have excellent intuition about rates of change at their fingertips, the abstraction of eigenvalues presents a road block». Our model includes three equilibrium states for the HPA system, one of which is unstable and the other two are stable. We developed a dynamical model of HPA axis to describe interactions between the key hormones and the GR with account of well known mediate feedback activity of cortisol. For example, a model is considered [3] where two attracting limit cycles arise in HPA system, so cortisol and ACTH oscillate to the beat of ultraradian (hourly) rhythms. Our model deals with two oscillating states. The state characterized by a lower cortisol level is associated with the normal state. Within this model, stress-induced secretion of CRH can trigger a transition between the normal and diseased states, respectively. A simple hyperbolic attractor of the dynamical system that contains two attractive fixed points and one repelling fixed point of codimension *1* (saddle point) forms slow asymptotic periodic oscillations of cortisol in the HPA axis.

Basic relations

In the present paper, we follow [4] and discuss the HPA axis model reported in [1] that accounts for the basic feedback mechanism and includes an intracellular glucocorticoid receptor GR as one of four state variables of the dynamical system, where variables [CRH], [ACTH], [GR] and [COR] represent concentrations. Here [GR] is related to cortisol. The resulting complex [COR–GR] determines general behaviour of solutions of the model. It is found that $\mathrm{GR} := \Phi[\mathrm{COR}])$, where Φ is a given nonlinear function (see [4], Fig. 1) which plays the main role in the quantitative behavior of limit distributions of cortisol in a physiological system.

We define $[\mathrm{GR}] := u$ and assume that $\Phi(I) \subset I$ for each $u \in I$, where I is an open bounded interval. Then all solutions of the problem are bounded for all $t > 0$. The phase diagram shows [4] that a state variable [GR] is a cubic type function of the concentration of cortisol $[\mathrm{COR}] := u$. Hence, for a certain stress region, the system exhibits two stable steady states and one unstable steady state.

It will be shown that the corresponding dynamical system in R^3 (three-dimensional space) can be reduced to the planar system with two delay equations:

$$\dot{x}(t) = y(t) - \rho_1 x(t), \tag{1}$$

$$\dot{y}(t) = -f\left(x(t-1)\right) - \rho_2 y(t) \tag{2}$$

where ρ_1 and ρ_2 are parameters. Function f is derived from the plot of function $\Phi : I \to I$, which is determined by the phase diagram of «pitchfork» type resulting from computer experiments in [5].

Thus, the HPA mathematical model can be reduced to the study of solutions of system (1), (2). Besides, the planar system can be reduced to an autonomous differential-difference delay equation of the second order:

$$\ddot{x}+\left(\rho_1+\rho_2\right)\dot{x}(t)+\rho_1\rho_2 x(t)=-f\left(x(t-1)\right),\quad \tau:=1 \tag{3}$$

that explains oscillating behavior of the solutions of differential-difference delay equations. It is known that the delay system has non-constant periodic solutions with a period greater then 2 [6].

With using these mathematical results, we found that there are slow oscillating asymptotically periodic solutions for the HPA axis, which describe distributions of cortisol. The role of delay in the HPA problem will be found. It turns out that oscillating solutions are stable if and only if

$$\tau_1<\tau<\tau_2, \tag{4}$$

where delay times τ_1 and τ_2 are estimated exactly, being dependent on given parameters of the physiological problem. Exact analytical parameter-dependent formulas for τ_1 and τ_2 will be derived.

Postulation of problem

The HPA axis has three components which represent the hypothalamus, the pituitary and adrenal. The equation for the hypothalamus is:

$$\frac{\mathrm{d}C}{\mathrm{d}T}=\frac{K_c+F}{1-\dfrac{O}{K_n}}-K_{cd}C, \tag{5}$$

where $-K_{cd}C$ describes constant degradation rate of CRH. In line with [1], we assume that $\dfrac{\mathrm{O}}{K_n}<<1$. Then it follows from (5) that

$$\frac{\mathrm{d}C}{\mathrm{d}T}=\left(K_c+F\right)\left(1+\frac{O}{K_n}\right)-K_{cd}C. \tag{6}$$

Here all undetermined constants can be found in [1]. Next, if $C=\dfrac{K_c+F}{K_{cd}}$ in (6), we can put $\dfrac{\mathrm{d}C}{\mathrm{d}T}\equiv 0$ with accuracy $O(\varepsilon)$, where $\varepsilon=\dfrac{\mathrm{O}}{K_n}$.

We write for the hypothalamus [1]:

$$\dot{c}=\frac{1+f}{1+\dfrac{o}{k_1}}-k_{cd}c, \tag{7}$$

for the pituitary

$$\dot{a} = \frac{c}{1+\dfrac{or}{k_2}} - k_{ad} a \,. \tag{8}$$

Equation (8) models the degradation rate of ACTH and ACTH production terms with a cortisol inhibition factor,

$$\dot{r} = \frac{(or)^2}{k+(or)^2} + k_{cr} - k_{rd} r \,. \tag{9}$$

For the adrenal we have

$$\dot{o} = -o + a(t-\tau) \tag{10}$$

with delay response τ.

If we put $c \coloneqq a$ in (8) (for unification with [7]) and consider only the equilibrium $\dot{c} = 0$, then we obtain the well-known model [7]:

$$\dot{a}(t) = \frac{A}{1+p_2 o(t) r(t)} - p_3 a(t) \,, \tag{11}$$

$$\dot{r}(t) = -\frac{p_4}{p_4 + (o(t)r(t))^2} + 1 + p_5 - p_6 r(t) \,, \tag{12}$$

$$\dot{o}(t) = -o(t) + a(t-\tau) \tag{13}$$

as a particular case of the model reported in [1]. Thus, we have a projection of trajectories of the dynamical system from R^4 into R^3. The assumption $\dot{c} = 0$ determines only zero line that describes curve

$$\frac{1+f}{1+\dfrac{o}{k_1}} - k_{cd} c = 0 \,. \tag{14}$$

The projection on R^3 requires at least $o/k_1 << 1$. We neglect this small term in the first approximation.

Remind [1] that stress applied to the HPA axis (f) stimulates the hypothalamus to secrete CRH(c). Further, CRH(c) signals the induction of ACTH synthesis (a) in the pituitary. Thus, our assumption means that the velocity of stimulation of the ACTH signals is constant, i.e. $c = \dfrac{1+f}{k_{cd}}$. Mathematically, it means that function $\mu = or$ can be considered as a parameter (at lest asymptotically). The effect of changing of parameters on c–zero line has been considered by Kim et al. [3].

Determination of fixed points for the HPA problem

It is known that these equations have three positive steady states (there is also a negative state which is not used). These steady states arise because of homodimerization of the GR with cortisol. From [1, Fig. 1] it follows that

$o = f_1(p_6)$ and $r = f_2(p_6)$, where another parameters are fixed. Here, f_1 and f_2 are multivalued functions.

$$\frac{\mathrm{d}C}{\mathrm{d}T} = \left(K_c + F\right)\left(1 + \frac{\mathrm{O}}{K_n}\right) - K_{cd}C\,. \tag{15}$$

Next, it follows from (6) that if $C = \dfrac{K_c + F}{K_{cd}}$, then we can set $\mathrm{d}C/\mathrm{d}T = 0$ with accuracy $\mathrm{O}(\varepsilon)$, where $\varepsilon = \mathrm{O}/K_n$.

As a result, we can consider the following approximation [7]:

$$\dot{a}(t) = \frac{A}{1 + p_2 o(t) r(t)} - p_3 a(t)\,, \tag{16}$$

$$\dot{r}(t) = -\frac{p_4}{p_4 + \left(o(t)r(t)\right)^2} + 1 + p_5 - p_6 r(t)\,, \tag{17}$$

$$\dot{o}(t) = -o(t) + a(t - \tau)\,. \tag{18}$$

The main role hear is played by equation (17), which describes the production of GR in the pituitary. The term $-\dfrac{p_4}{p_4 + (o(t)r(t))^2} + 1$ is in Michaelis–Menten form (see [1]) because we assume that the bound glucocorticoid receptor (*or*) in the dimensionless form is dimerized with fast kinetics, so that the amount of dimers is in constant quasi-equilibrium and ones depends on the excess of *or*. The model also assumes that cortisol (*o*) and the glucocorticoid receptor (*r*) are bound to each other with very fast kinetics, which is compared to the rate of the change of 4 state variables (*A*, *C*, *O*, and *R*), so that *OR* stays in quasi-equilibrium as well. These are reasonable assumptions, because of high affinity, the receptor-ligand kinetics is often much faster than enzyme kinetics, as is assumed in Michaelis–Menten equation (see [1]). Equation (16) models linear production term $K_c r$ and degradation term $-K_{rd}R$ for pituitary GR production. Below, in the dimensional form for the model, these coefficients are defined as 1 and p_6, respectively.

Remark 1

Note that (*c*) represents the level of circuiting CRH, (*a*) defines the level of circuiting ACTH, (*r*) describes the level of glucocorticoid receptor in the pituitary, and (*o*) is the level of circuiting cortisol. In equations for (*a*) and (*r*), the cortisol-receptor complex (*or*) is assumed to form and dissociate under fast dynamics [3]. Below it will be proved mathematically to be true indeed, because there are so-called slow oscillating distributions of cortisol [3]. It has been shown that this level can be approximated as «steady state» by the production (*or*).

Indeed, let us define $\mu = or$. Then the origin problem in R^3 can be unfolded as a system in R^3, so that

$$\dot{a} = \frac{A}{1 + p_2\mu} - p_3 a\,, \tag{19}$$

$$\dot{r} = -\frac{p_4}{p_4 + \mu^2} + 1 + p_5 - p_6 r\,, \tag{20}$$

$$\dot{o} = -o + a\,, \tag{21}$$

$$\dot{\mu} = \dot{o}r + \dot{r}o\,, \tag{22}$$

where, in (21), $a := a(t)$ or $a := a(t-\tau)$.

It follows from these equations that the fixed points are located at the curves

$$a = \frac{1}{p_3}\left(\frac{A}{1 + p_2\mu}\right), \tag{23}$$

$$r = \frac{1}{p_6}\left(-\frac{p_4}{p_4 + \mu^2} + 1 + p_5\right). \tag{24}$$

Since the fixed points are positioned at diagonal $o = a$, by multiplying these relations and substituting $o = a$, and putting at a fixed point $\dot{\mu} = 0$, we obtain that μ is a solution of the fourth order algebraic equation. Indeed,

$$or = \mu = \frac{1}{p_6 p_3}\left(\frac{A}{1 + p_2\mu}\right)\left(-\frac{p_4}{p_4 + \mu^2} + 1 + p_5\right). \tag{25}$$

Let $\nu = \dfrac{A}{p_6 p_3}$. Then from (25) we get

$$p_4\mu^4 + \mu^3 + \left(p_2 p_4 - (1 + p_5)\right)\mu^2 + p_4\mu - \nu p_5 p_4 = 0\,. \tag{26}$$

By Descartes rule, this equation has 3 or 1 positive roots and 1 negative root which can not be considered. Descartes rule means that the number of positive roots of the polynomial is either equal to the number of sign differences between the coefficients, or it is less of it by an even number. So, if we assume that

$$p_2 p_4 < 1 + p_5\,, \tag{27}$$

then equation (26) has 3 positive roots μ_1, μ_2, μ_3. Then we can find three fixed points of the problem from (23), (24).

Thus, there are $\dot{\mu} = 0$ on a hyperplane in R^4-space that is included in R^4-space, where μ can be considered as a parameter. Since the basis in R^4 is not a family of independent vectors, we can use this observation to find conditions when the trajectories of the dynamical system in R^4 are attractive by trajectories in R^3. If this is true, then function $\mu(t)$ in R^4 is a constant function in R^3. A condition when it is possible can be easily found. Indeed, let λ_1, λ_2, λ_3, λ_4 be the eighenvalues of the problem. It means that

$$\dot{a} = \lambda_1 a, \quad \dot{r} = \lambda_2 r, \quad \dot{o} = \lambda_3 o, \quad \dot{\mu} = \lambda_4 \mu o \,. \tag{28}$$

Then

$$\dot{\mu} = \lambda_4 \mu = \dot{o} r = (\lambda_2 + \lambda_3)\lambda \,. \tag{29}$$

It follows from (29) that if $\lambda_2 + \lambda_3 < 0$, then $\dot{\mu} \to 0$ as $t \to +\infty$. So μ can be considered as a parameter in asymptotic sense.

Geometric method of determination of the fixed points of the problem

Now we assume that there is a component $o = o^*$ of a fixed point in R^3. Then we see from equation (20) for cortisol that $\dot{r} \equiv 0$ if $G(r, o) \equiv 0$. So, the (o, r)-nullcline structure can be found from (17) that is determined as a curve $r := r(o)$ such that $G(r(o), o) \equiv 0$ for each admissible o within some interval (the corresponding numerical simulation is reported in [3, Fig. 4]. To make it, we assume that there is a component of fixed

$$G(r,o) := -p_6 o^2 r^3 + (1 + p_5) o^2 r^2 - p_4 p_6 r + p_4 p_5 = 0 \tag{30}$$

where o can be considered as a parameter. Thus, there is a multi-valued curve $r := r(o)$ such that $G\big(r(o), o\big) \equiv 0$ for every positive fixed o. This curve has been found by numerical simulation in [3], Fig. 4. The curve is S-shaped as a graphic of a cubic polynomial.

Applications of the singularity theory for the HPA problem

If we find from (29) the curve $S = r(o)$, then $\dot{r} = 0$ on this curve that follows from the second equation of the HPA problem for the function $r(t)$. The results of computer experiments can be found in [3]. On this *S*-shaped curve that tends to bistability, function $r(t)$ is constant.

The behavior of GR can be analyzed by the singularity theory. The graphic $r := r(o)$ is multi-valued and S-shaped as shown, for example, in [5], Fig. 3. It follows from [8] that there is irreversibility if

$$G = G_r = G_{rr} = 0, \quad G_{rrr} \neq 0 \,. \tag{31}$$

As $G(r, o) = 0$, there are one or three fixed points for every fixed positive a. It follows from equation $G_{rr} = 0$, i.e.

$$-3 p_6 o^2 r + (1 + p_5) o^2 = 0, \quad o \neq 0 \tag{32}$$

that we have the vertical inflection point value $r = \dfrac{1 + p_5}{3 p_6}$ here, which is independent of o as a parameter. Ignition and extinction points in the $(r - o)$ locus (see [5]) are determined by the solutions $G = G_r = 0$ with $G_{rr} \neq 0$.

They satisfy a quadratic equation

$$-(1 + p_5) o^2 r^2 + 2 p_4 p_5 r - 3 p_4 p_5 = 0 \tag{33}$$

that results in

$$r_{1,2} = \frac{-p_4 p_5 \pm \sqrt{(p_4 p_5)^2 - 3(1+p_5) p_4 p_5}}{-(1+p_5)}. \tag{34}$$

In the case of bistability, these points separate three fixed states (one unstable saddle point is between two stable states). We see that inequality

$$(p_4 p_5)^2 \geq 3(1+p_5) p_4 p_5 \tag{35}$$

must be satisfied for the bistability to exist (it is the necessary condition).

Note that according to Descartes rule of signs, the number of positive roots of a polynomial is equal to the number of sign changes in the coefficients or less of it by a multiple of 2. Hence polynomial (30) has one or three positive roots. These roots are positioned at the curve $r(o)$. The intersection of this curve with the line $o = a$, which follows from (18), yields $\mu = ar(a)$. Here $\mu = (\mu_1, \mu_2, \mu_3)$. With using (32), we find the fixed points of the problem, which are $p_k = \left(a_*^k, a_*^k, r_*^k = r(a_*^k)\right), \quad k = 1,2,3$.

Note also that according to interpretation in [1], Fig. 3, the variations of the steady state for GR and cortisol *r* are obtained, respectively, with a as a parameter. There are three intervals I_1, I_3 and I_2. If $a \in I_1 \bigcup I_3$, then there are two attractive fixed points. If $a \in I_2$, we obtain a repelling fixed point.

2D nonlinear dynamics

Let us consider the system of equations

$$\dot{o}(t) = -o(t) + a(t-\tau), \tag{36}$$

$$\dot{a}(t) = -f\left[o(t)\right] - p_3 a(t). \tag{37}$$

Then

$$\dot{a}(t-\tau) = -f\left[o(t-\tau)\right] - p_3 a(t-\tau). \tag{38}$$

Define $a(t-\tau) = y(t)$. Then it follows from (60) that

$$\dot{y}(t-\tau) = -f\left[o(t-\tau)\right] - p_3 y(t). \tag{39}$$

In (57) we define (for unification with [6]) $o(t) = x(t)$. Then (58), (61) can be written as

$$\dot{x}(t) = y(t) - x(t), \tag{40}$$

$$\dot{y}(t-\tau) = -f\left[o(t-\tau)\right] - p_3 y(t), \tag{41}$$

$$\dot{y}(t) = y(t) - x(t). \tag{42}$$

Consequently, the first equation can be written as

$$\dot{y}(t) = \frac{A}{1 + p_2 o(t) r\left(o(t)\right)} - p_3 y(t). \tag{43}$$

Note that on every plane $\dot{y}(t) \equiv 0$, the following functional relation $r(t) \equiv \Phi\big(o(t)\big)$ is satisfied, where Φ is a known irreversible function. Remind that function Φ represents the glucocorticoid receptor (GR) that is included in the HPA axis (see [1, Fig. 3(a)]) that involves the glucocorticoid. The nonlinear effect arises when GR homodimerizes (after cortisol activation) and induces its own synthesis in the pituitary. The form of graphics $\Phi(o)$ plays the main role in the qualitative study of solutions. The S-shaped graphic allows finding of three fixed points. Two of these fixed points are attracting, but one of the points o_* must be repelling in R^1.

Indeed, it will be shown below that if o_* is attracting, there are four fixed points in reality (see the previous stable solutions). So there are no oscillating solutions. If the unique fixed point o_* is repelling, then this point plays the role of the separator. The behavior of a solution depends on the amplitude of the initial data which is given within interval $[-\tau, 0)$. Let $h(t)$ be the initial function within $[-\tau, 0)$. Then if $0 < h(t) < o_*$, the solution tends to a constant solution $o(t) \to o_1 < o_3$ as $t \to +\infty$. If $h(t) > o_*$ on interval $-\tau, 0)$, then $o(t) \to o_1 < o_3$ as $t \to +\infty$. As a result, the existence of both delay and repelling fixed points results in the possibility of oscillating solutions of the problem if the initial data on $-\tau, 0)$ are large enough.

Planar case on RG null-isocline

Now we return to the mathematical aspects of the problem i.e. to equation (43). Define

$$-f(o) := \frac{A}{1 + p_2 o r(o)}, \tag{44}$$

where $r(o)$ is defined by RG form of the RG curve. Then equation (42) can be rewritten as

$$\dot{y}(t) = -f(o) - p_3 y(t). \tag{45}$$

Next, an important observation is that both equations (43) and (60) are equivalent to the system of equations

$$\dot{x}(t) = y(t) - \rho_1 x(t), \tag{46}$$

$$\dot{y}(t) = -f(x(t-\tau) - \rho_2 y(t), \tag{47}$$

where for (45) we put $\rho_1 = 1$, $\rho_2 = p_3$, $\tau = 1$. Then it follows from [6] that system (46), (50) has a monotonic periodic solution with a period greater than 2 and 2τ for the origin physiological problem, respectively.

Here, the following conditions must be satisfied: (i) a and b are positive constants, (ii) $f(u) > 0$ for all $u \neq 0$, (iii) there is a positive constant χ such that $f(u) \geq -\chi$ for all u,

$$\dot{f}(0) > \frac{(\rho_1 + \rho_2)\gamma}{\sin\gamma}, \tag{48}$$

Where γ satisfies $0 < \gamma < \pi$, and

$$\coth\gamma = \frac{1}{\gamma}(\gamma - \rho_1\rho_2)(\rho_1 + \rho_2). \tag{49}$$

Remind that $\rho_1 = 1$ and $\rho_2 = p_3$ for the physiological problem. Hence, condition (i) is satisfied. Next, the inequality (60) becomes

$$\dot{f}(0) > \frac{(1 + p_3)\gamma}{\sin\gamma}. \tag{50}$$

Note that there is only a unique fixed point 0 as reported in [6]. In our situation, there are three fixed points (o_1, o_2, o_3), where o_1 and o_3 must be attractive fixed points, and $o_2 = o_*$ is a repelling fixed point. So that inequality (62) becomes

$$\dot{f}(o_*) > \frac{(\rho_1 + \rho_2)\gamma}{\sin\gamma}. \tag{51}$$

Further, the point o_* must be repelling. For example, we obtain $\dot{f}(o_*) > 1 + p_3$ in the limit $\gamma \to 0$ and, hence, the condition of the local instability is satisfied. Since, $p_3 \geq 0$, this fixed point must be repelling at least for small δ. In conclusion, the condition (iii) is the condition of local instability as it will be shown below.

Analysis

Define $\alpha = \rho_1 + \rho_2$, $\beta = \rho_1\rho_2$, $\nu = \dot{f}(0)$. Then the characteristic equation is

$$\lambda^2 + \alpha\lambda + \beta + \nu e^{-\lambda} = 0, \tag{52}$$

where we assume that $\tau = 1$. If $\tau \neq 1$ then the problem is reduced to the characteristic equation:

$$z^2 + \alpha\tau z + \beta\tau^2 + \nu\tau^2 e^{-z} = 0, \tag{53}$$

where $z = \lambda\tau$, $\nu \to \nu\tau^2$, $\alpha \to \alpha\tau$, and $\beta \to \beta\tau^2$, and we assume that $\tau \neq 0$.

Further, we use the results reported in [6], Lemma 1. If α, β, ν are positive, and if $\alpha^2 \geq 2\beta$, then the following three conditions are equivalent: (1) Equation (52) has at least one solution. (2) The characteristic equation has precisely one solution λ with $\Re\lambda > 0$ and $0 < \Im\lambda < \pi$. (3) The following inequality is true

$$\nu > \frac{\alpha\nu_1}{\sin\nu_1}, \tag{54}$$

where $0 < \nu_1 < \pi$ and

$$\coth\nu_1 = \frac{1}{\alpha}\left(\nu_1 - \frac{\beta}{\nu_1}\right). \tag{55}$$

Note that there are many details about the behavior of trajectories of the dynamical system. We formulate this behavior as distributions of concentrations of hormones a and o on the $(o-a)$-plane, where o is the distribution of cortisol. For example, there is an estimation

$$\dot{f}(0) > \frac{\rho_1\rho_2}{\exp\left(\min(\rho_1,\rho_2)\right)-1}, \tag{56}$$

where $0 \to o_*$ and $\rho_1 = 1$, $\rho_2 = p_3$ so that

$$\dot{f}(o_*) > \frac{p_3}{\exp\left(\min(1,p_3)\right)-1}. \tag{57}$$

Then a component $o(t)$ is characterized as follows: 1) zeroes for a graphic $o(t)$ form an infinite series t_k, $k = 1,2,\ldots$, with $o(t_k) = 0$, $t_{k+1} - t_k > 1$ and $\dot{o}(t_{2k-1}) < 0$, $\dot{o}(t_{2k}) > 0$, and $\dot{o}(t_{2k-1}) < 0$, $\dot{o}(t_{2k}) > 0$, and $a(t_{2k-1}) < 0, a(t_{2k}) > 0$, and $a(t_{2k-1}+1) < 0$, $a(t_{2k}+1) > 0$; 2) function $e^{\alpha t}o(t)$ is monotonic and increasing on interval $(t_{2k}, t_{2k}+1)$ and monotonically decreasing on $(t_{2k-1}, t_{2k-1}+1)$, where $\alpha = 1 + p_3$ (see Fig. 1).

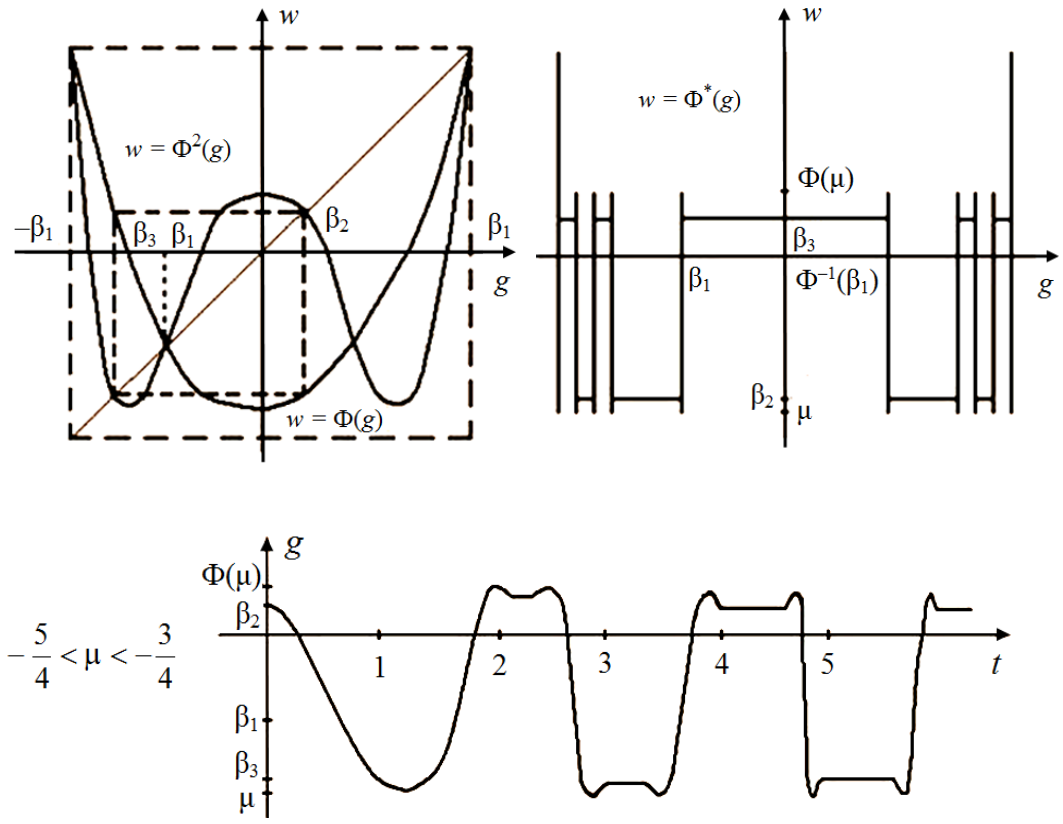

Fig. 1. Slow oscillating distributions of cortisol

Necessary and sufficient condition for the existence of slow periodic solutions

If $\tau \neq 1$, then we obtain the characteristic equation

$$z^2 + \alpha\tau z + \beta\tau^2 + \nu\tau^2 e^{-z} = 0, \tag{58}$$

where $z = \lambda\tau$. Define $\hat{\alpha} = \alpha\tau$, $\hat{\beta} = \beta\tau^2$ and $\hat{\nu} = \nu\tau^2$. Next, we must verify the assumption $\hat{\alpha}^2 > 2\hat{\beta}^2$ from [6], Lemma 1. Evidently that this assumption is satisfied for every $\tau \neq 0$.

Further, we assume that

$$\pi^2 + \frac{\hat{\alpha}^2}{4} - \hat{\beta}^2 > 0. \tag{59}$$

The necessary condition of delay follows from (59)

$$\tau < \frac{2\pi}{\sqrt{4\beta - \alpha^2}}. \tag{60}$$

We obtain from (60) that $2\beta < \alpha^2 < 4\beta$ that results in the natural condition $p_3 > 1$.

The condition (59) allows application of Lemma 1 (see [6]). It means that characteristic equation (58) has precisely one solution z with $\Re z > 0$ and $0 < \Im z < \pi$. Here, $\hat{\nu}$ must be such that

$$\hat{\nu} > \frac{\hat{\alpha}\hat{\nu}_1}{\sin\hat{\nu}_1}, \tag{61}$$

where $0 < \hat{\nu}_1 < \pi$, and

$$\coth\hat{\nu}_1 = \frac{1}{\alpha}\left(\hat{\nu}_1 - \frac{\beta}{\hat{\nu}_1}\right) \tag{62}$$

(see [6], conditions (2), (3) from Lemma 1).

It follows from (62) that

$$\nu\tau^2 > \frac{\alpha\nu_1\tau^3}{\sin\nu_1\tau^2}. \tag{63}$$

In the limit $\tau \to 0$,

$$\tau > \frac{\alpha}{\nu} + O(\tau^2). \tag{64}$$

Remind that $\nu = \dot{f}(o_*)$, where o_* is the repelling fixed point of f. Being combined with (62) it yields

$$\frac{1 + p_3}{\dot{f}(o_*)} < \tau < \frac{2\pi}{\sqrt{4\beta - \alpha^2}}. \tag{65}$$

Inequality (65) determines the necessary and sufficient conditions for the existence of slow periodic solutions for the HPA problem in 2D approximation.

Conclusion

In this paper, physiological and mathematical mechanisms of formation of ultraradian oscillations in the HPA axis have been considered. It is shown that the main role is played by the nonlinear connection between cortisol COR and the GR that forms a homodimer [9]. A conception of transcriptional regulation is that the GR feedback control works rather slowly as compared to other cellular processes.

The corresponding differential-difference equations with the delay argument have slow oscillating periodic solutions. The delay has been included because, for example, in mammalian cells, one can expect at least a delay of the down regulation in the range of 15 minute up to 2 hours (see [4]). It is proved that this hypothesis has been confirmed as slow oscillating 2τ (or larger) periodic distributions of cortisol at least mathematically (Fig. 1). Here we follow a mechanistic ODE system model of the glucocorticoid feedback mechanisms within the anterior pituitary gland cell, with addition of the delay τ to this model.

It is shown that an important factor is the consequence between extracellular events such as changes in the CRH and cortisol induced inhibitory effect on anterior pituitary gland cells, which already occurs after a few seconds [11,12]. As a result, slow oscillating periodic solutions of the mathematical mode explain qualitatively a phenomenon that can not be explained by the genomic feedback mechanism [4]. Exact interval $\tau_1 < \tau < \tau_2$ for existence of slow oscillating periodic distributions for cortisol has been found.

1. *S. Gupta, E. Aslakson, B.M. Gurbaxani, S.D. Vernon*, Theor. Biol. Med. Model. **4**, 8 (2007).
2. *B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts, P. Walter*, Molecular Biology of the Cell, Garland Science, New York (2007).
3. *L.U. Kim, M.R. D'Orsogna, T. Chou*, Computational Psychiatry **2**, 28 (2018).
4. *C.A. Zarzer, M.G. Puchinger, G. Kohler, P. Kugler*, Theoretical Biology and Medical Modelling **10**, 65 (2013).
5. *S. Jelic, Z. Cupic, L. Kolar-Anic*, Mathematical Biosciences **197**, 173 (2005).
6. *U. an der Heiden*, Journal of Mathematical Analysis and Applications **70**, 599 (1979).
7. *J. Rankin, J.J. Walker, R. Windle, S.L. Lightman, J.R. Terry*, PLoS ONE 7 (2): e30978. DOI: 10.1371/journal.pone.0030978.
8. *P. Gray, S.K. Scott*, Chemical Oscillations and Instabilities. Non-linear Chemical Kinetics, Clarendon, Oxford (1990).
9. *J. Drouin, Y.L. Sun, S. Tremblay, P. Lavender, T.J. Schmidt, A. de Léan, M. Nemer*, Molecular Endocrinology **6**, 1299 (1992).
10. *Computational* Neuroendocrinology (Wiley-INF Masterclass in Neuroendocrinology Series), Duncan J., MacGregor, Gareth Leng (Eds.), Wiley Bleckwell (2016).
11. *A.W. Norman, M.T. Mizwicki, D.P.G. Norman*, Nat. Rev. Drug. Discov. **3**, 27 (2004).
12. *R. Lösel, M. Wehling*, Nat. Rev. Mol. Cell. Biol. **4**, 46 (2003).

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МЕДЛЕННЫЕ ПЕРИОДИЧЕСКИЕ ОСЦИЛЛЯЦИИ В СИСТЕМЕ ГИПОТАЛАМУС–ГИПОФИЗ–НАДПОЧЕЧНИКИ

Рассмотрена структурированная модель системы гипоталамус–гипофиз–надпочечники (ГГН), которая включает в себя глюкокортикоидный рецептор (ГР). Модель учитывает нелинейную динамику синтеза ГР гипофизом. Нелинейный эффект возникает по той причине, что ГР гомодимеризуется после активации кортизола и инициирует свой собственный синтез гипофизом. Гомодимеризация дает возможность реализации двух стабильных устойчивых состояний (низкого и высокого) и одного нестабильного. Модель включает в себя также задержку воздействия стресса. Установлено, что конкуренция между траекториями динамической системы, вызванная нестабильным многообразием и значением времени задержки τ, приводит к медленным периодическим осцилляциям кортизола с периодом, большим, чем 2τ Показано, что осцилляции существуют только в интервале $\tau_1 < \tau < \tau_2$, получены точные формулы для τ_1 и τ_2. Осцилляции появляются, когда начальное значение стресса становится выше некоторого порога.

Ключевые слова: гипоталамо-гипофизарно-надпочечниковая ось, асимптотические периодические осцилляции, отрицательная обратная связь, дифференциально-разностные уравнения задержки, нормальное состояние

Рис. 1. Медленные колебательные распределения кортизола