Mathematical Model of Thyroid Function

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Abstract: We developed a mathematical model of thyroid function, representing a Cauchy problem for an ordinary differential system. It takes into consideration its possible dysfunctions. The article suggests options of treatment planning, which allow to estimate both time of treatment and economic expenses.

Key words: Mathematical modeling • Differential equations • Thyroid

INTRODUCTION

Thyroid in mammals’ organisms carries out a functional role connected with the morphosis. It digests iodine, which is vital, produces hormones regulating different biochemical reactions and determining normal functioning of an organism. Its dysfunction leads to organism’s metabolic processes disorder and various iodine deficiency disorders. Mathematical models published in literary sources [1-4] describe as a rule iodine metabolism in an organism, not the work of thyroid itself. The most complete mathematical model of thyroid suggested by [5] as an element of endocrine system represents the system of ten ordinary differential equations, containing over 50 constants. Given so many variables and constants, determination of the latter on basis of experimental information is not a simple task – perhaps even an unsolvable one. Synthesis and release of hormones are complicated processes, include many biochemical reactions. Mathematical model of thyroid, contained in the work [6] suggested by the authors, considers main reactions taking their places in it: intake of iodine, its banding with thyroglobulin and subsequent formation and accumulation in thyroid of the hormone $T_4$ [7-9]. The model represents a Cauchy problem for a system of four ordinary differential equations.

Main Biochemical Reactions: The thyroid in the model is a two-layer globoid. The outer (the first chamber) and the inner (the second chamber) layers are separated by a membrane. Iodine ($I$) gets into the outer layer through its outer surface; then iodine after its banding with thyroglobulin ($Tg$) located in this layer gets into the inner layer through an isolating membrane, which permeability is $P_{Tg}$. Iodine does not get into the inner layer. In the inner layer thyroglobulin takes part in hormone ($T_4$) formation reaction; this hormone is reserved banded with thyroglobulin. When the hormone level in blood serum decreases, the hormone detaches from thyroglobulin and out of the thyroid in unbound form gets into blood flow through the outer membrane with permeability $P_{T_4}$ [7, 10 - 12]. Thyroglobulin is reserved in the thyroid, it does not get into outside medium.

Mathematical Model: When mathematical model formulating, we use approaches analogous to those which were used in [1-5]. Let it be:

\[ u_I^0 \] - Iodine concentration in outer flow, getting into the first chamber with velocity $v$,
\[ u_{Tg} \] - Thyroglobulin concentration in the first chamber,
\[ u_{T4} \] - Thyroglobulin concentration in the second chamber,
\[ P_{Tg} \] - Thyroglobulin permeability of the membrane separating the chambers,
\[ P_{T4} \] - $T_4$ hormone permeability of the membrane separating the chambers.

In respect of the given designations, reactions proceeding in the first chamber are governed by equations:
\[
\frac{du_I}{dt} = v(u_I^0 - u_I) - a/u_I^0 \frac{u_Tg}{b_2 + u_Tg}, \\
\frac{du_{Tg}^i}{dt} = \alpha/a_u \frac{u_{Tg}^i}{b_2 + u_{Tg}^i} - P_{Tg} u_{Tg}^i. \\
\]

The summand \(a u_I^0 \frac{u_Tg}{b_2 + u_Tg}\) in the first equation is the velocity of banding iodine and thyroglobulin and the summand \(\alpha/a_u \frac{u_{Tg}^i}{b_2 + u_{Tg}^i}\) in the second equation is the velocity of thyroglobulin formation. The summand \(P_{Tg} u_{Tg}^i\) in the second equation describes the velocity of thyroglobulin leaving through the colloid membrane with permeability \(P_{Tg}\) for thyroglobulin into colloid.

Reactions proceeding in the second chamber are governed by equations:

\[
\frac{d u_{Tg}^i}{dt} = -a_{2Tg} u_{Tg}^i \frac{u_{Tg}^i}{b_3 + u_{Tg}^i} + P_{Tg} u_{Tg}^i, \\
\frac{d u_T^4}{dt} = \beta a_{2Tg} u_{Tg}^i \frac{u_{Tg}^i}{b_3 + u_{Tg}^i} - P_{Tg} u_{Tg}^i. \\
\]

In the first equation the summand \(P_{Tg} u_{Tg}^i\) is the velocity of thyroglobulin getting out of the first chamber into the second one, the summand \(-a_{2Tg} u_{Tg}^i \frac{u_{Tg}^i}{b_3 + u_{Tg}^i}\) is the velocity of spending of thyroglobulin for hormone formation in the second chamber, the summand \(\beta a_{2Tg} u_{Tg}^i \frac{u_{Tg}^i}{b_3 + u_{Tg}^i}\) is the velocity of the hormone formation and the summand \(P_{Tg} u_{Tg}^i\) is the velocity of \(T4\) hormone getting into blood flow through the colloid membrane with permeability \(P_{Tg}\) for hormone. In equations (1)-(2) \(a_1, a_2, b_1, b_2, a_3, a, \beta\) are positive constants.

**Critical Points:** The equations system (1) – (2) has a critical point \(u_I = u_I^0, u_{Tg} = u_{Tg}^i, u_T^4 = u_T^4 = 0\). Critical points will be stable if eigenvalues of Jacobian matrix of the right-hand member of the equations (1)-(2) have negative real parts [13]. Eigenvalues of Jacobian matrix of the equations (2) in this point are equal to \(\lambda_1 = -v, \lambda_2 = a_{1Tg} a_{2Tg} - P_{Tg} u_{Tg}^i.\) When the inequation \(u_I^0 < b_2 a_{1Tg} a_{2Tg}/P_{Tg}\) is completed, this point will be stable.

The second critical point satisfies the equations system:

\[
u_{Tg} = \frac{v (u_I^0 - b_2 - P_{Tg})}{\alpha a_1}, \quad u_I = P_{Tg} \left(\frac{b_2 + u_T^4}{a_1 + v}\right), \\
u_T^4 = \frac{b_3 + u_T^4}{a_2 a_{2Tg}} P_{Tg} u_{Tg}^i. \\
\]

This point has physical meaning when the following inequation is completed:

\[
u_I^0 > b_2 a_{1Tg} a_{2Tg}/P_{Tg}. \\
\]

Four eigenvalues of Jacobian matrix of the right-hand member of the equations system (1)-(2) are the roots of quadratic equations:

\[
\lambda^2 + \lambda \left(\frac{v u_I^0 + P_{Tg} (1 - b_2)}{b_2 + u_T^4}\right) + a_{1Tg} u_{Tg}^i - P_{Tg} = 0, \\
\lambda^2 + \lambda \left(P_{Tg} (1 - b_3) + a_{2Tg} u_T^4 + a_{3Tg} u_T^4\right) + a_{2Tg} u_T^4 P_{Tg} = 0. \\
\]

As it follows from the equations (5)-(6) analysis, in the critical point (3) eigenvalues either will be negative or will have negative real parts. That is, when the condition (4) is fulfilled, this steady-state will be stable [13].

In respect of relative values of constants \([1, 5]\) (which were published in literary sources), entered into the equations (1)-(2), the model accepts the following: \(a_1 = 50, b_2 = 1.1, \alpha = 0.2, \beta = 5.5\). In view of the accepted constant pool, the model time measure unit corresponds to twenty-four hours and substances concentration are considered to be dimensionless.

**Thyroid Dysfunction:** Dysfunctions can have internal and external reasons. Some of internal reasons are, first of all, changes of reactions rate and system’s mechanical characteristics, changes in properties of external and
internal membranes. External reasons are change of iodine entering from outside and influence of different harmful substances [17], having an impact on proceeding of biochemical reactions in an organism [18, 19].

One of the main dysfunctions is change of amount of iodine entering the thyroid. According to correlations (3), this is accompanied by increase or decrease of the hormone release. Normal qualities can be recovered by an external influence (treatment [20]). We consider two options. With the first option, influence starts at the beginning of the dysfunction (early detection), with the second one – after achieving the maximum dysfunction (late detection).

Let additional iodine enter the thyroid, in the amount of $u_I^c$; this iodine brings it out of the steady state. Change of its amount is accounted for administering preparations with the concentration Drug. Model of thyroid function (1)-(2) in view of these dysfunctions will be as follows:

$$\frac{du_I}{dt} = v(u_I^c + u_T^p - u_I) - a u_I u_T^p + \frac{u_T^p}{b_2 + u_T^p},$$

$$\frac{d u_T^g}{dt} = \alpha a u_I u_T^g + \frac{u_T^g}{b_2 + u_T^g} - a u_T^g u_T^4 + \frac{u_T^4}{b_3 + u_T^4},$$

$$\frac{d u_T^4}{dt} = \beta a u_T^4 + \frac{u_T^4}{b_3 + u_T^4} - P_{14} u_T^4 u_T^4,$$

$$\frac{d u_T^p}{dt} = -u_T^p f(t, \text{Drug}).$$

(7)

In these equations $u_T^p(t, \text{Drug})$ is the velocity of decrease of additional iodine concentration due to administered preparations. It is estimated that this velocity is proportional to the amount of administered preparations and additional iodine. Preparations are administered in the time interval $[t_1, t_2]$ under the rule $f(t, \text{Drug})$. Total amount of administered preparations is calculated by formula $M = \int_{t_1}^{t_2} f(t, \text{Drug}) dt$. As functions $f(t, \text{Drug})$ we considered two options:

$$f(t, \text{Drug}) = \text{Drug}$$

(8)

$$f(t, \text{Drug}) = \text{Drug} \frac{1 + \sin \omega t}{2}.$$  

(9)

The first option corresponds to an occasion when preparation’s dosage is constant, the second one – to when preparations’ dosage changes with time.

As initial conditions we considered two options. With the first option, at the time moment $t = t_1$ the system is in stationary equilibrium position, described by the correlations (3). At this time moment the thyroid dysfunction occurs, so the amount of additional iodine is $u_I(t = t_1) = u_I^c$. And simultaneously the preparation starts to be administered. This occasion models an early detection of the thyroid dysfunction. With the second option, it is estimated that at the time moment $t = t_1$ the system is in stationary equilibrium position, described by the correlations (3) with the entered iodine concentration which is equal to $u_I^c + u_T^p$. This is an occasion of a late detection of dysfunction.

Preparations spending in the first occasion ((8)) is defined as $M = \text{Drug} \left( t_2 - t_1 \right)$ and in the second one ((9))

$$M = \text{Drug} \left[ \frac{1}{2} (t_2 - t_1) + \frac{1}{2\omega} (1 - \cos \omega (t_2 - t_1)) \right].$$

(10)

Results of numerical modeling (solution of equations (7)) for case $u_I^c = 1, v = 1, a_1 = 50, a_2 = 0.2; a_3 = 1; b_1 = 0.3; b_2 = 5.5; P_{14} = 1; u_T^p$ are shown on Figures 1-2.

For the case of an early detection you can see the change of T4 hormone release in the Fig. 1. The curve $\text{Drug} = 0$ corresponds to disrupted release of the hormone in case of absence of preparations’ influence; the curve $\text{Drug} = (1 + \sin(\omega t))/2$ corresponds to the case of administering preparations with changing dosage; the curve $\text{Drug} = 1$ corresponds to the case of administering preparations with constant dosage. Time of preparations supply is $t \in [1, 9]$. Preparation spending in the first case was 5.6 units and in the second case – 8 units.

Fig. 2 shows the case of a late detection. The curve $\text{Drug} = 2$ in the time interval [0, 1] corresponds to steady state with increased amount of iodine being entered. The curve $\text{Drug} = (1 + \sin(\omega t))/2$ corresponds to the case of administering preparations with changing dosage and the curve $\text{Drug} = 1$ corresponds to the case of administering preparations with constant dosage $\text{Drug} = 1$ in the interval (1, 9). The curve $\text{Drug} = 2$ corresponds to the case of administering preparations with changing dosage $\text{Drug} = 2$ in the time interval (1, 3). Preparation spending in the first case was 5.6 units, in the second – 8 units and in the third – 4 units. Both in cases of early and late detection, the minimum spending occurred with the changing dosage of preparation. The data for the time of transition from the medicine taking effect to normal functional status coincide with the results obtained in [21, 22] – transition from disturbed state to undisturbed state takes 8 – 10 units of time and the amount of the hormone getting into blood flow and the amount of thyroglobulin being free in the thyroid are related as 4:1.
CONCLUSION

The mathematical model of thyroid function that we have developed describes main hormone synthesis biochemical reactions and is consistent with experimental information of clinical trials concerning output characteristics. Mathematical modeling of possible thyroid dysfunctions and options of their treatment showed the opportunity to plan treatment with due consideration of necessary economical and time resources.

REFERENCES


