A Modified Mathematical Model Interpreting the Quantitative Behavior of Testosterone in the Male Hormonal Regulation

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***Abstract*:** *We propose a modified mathematical model for male sex hormone regulation taking into account the quantitative behavior of two forms of testosterone hormones. The model is able to present a significant relation between total testosterone and bound testosterone levels in the hypothamic-pituitary-gonadal axis. Moreover, we show the numerical simulations of the model to illustrate the possible behaviors.*

Keywords: *Hormone, Time delay, Testosterone, SHBG, Hormonal regulation*.

1. Introduction

Hormones are chemical substances which are produced by the glands in the bodily system. It has many functions including control and regulation the activity of certain tissues or organs. In the reproductive system, sex hormones are responding to control the development of primary and secondary sexual characteristics.

In male, testosterone is the majority of sex hormone secreted into the bloodstream by the male sex gland. This male sex hormone is synthesized and secreted primarily by Leydig cells in the testis. It plays a crucial role in the development and maintenance of many male characteristics. The body carefully regulates the production of testosterone in order to ensure normal development and regulation of male reproductive system [1]. Testosterone synthesis is controlled by biological mechanism in the reproductive hormonal axis which contains three main components: the hypothalamus, the pituitary gland and the gonads. Hormones which are produced in this axis include gonadotropinreleasing hormone (GnRH), luteinizing hormone (LH) and testosterone (T). These hormones are implicated in regulation reproductive operation via a complex feedback loop. GnRH is released by the hypothalamus in a episodic manner. It then triggers the pituitary gland to produce and secret LH into the blood, which activates the enzymatic conversion of cholesterol into testosterone in the Leydig cells. Testosterone is secreted in pulsatile pattern. Its levels have rapidly acting feedback activity at both hypothalamic level and pituitary level in order to maintain adequate levels of the hormones in the male reproductive system [2,3] shown in Fig 1. In normal men, plasma levels of testosterone range from 270 to 1,070 nanogram/deciliter (ng/dl) with an average level of 679 ng/dl [4, 5]

After this male sex hormone is released, testosterone, it is principally bound to proteins in the blood, most of which is sex hormone binding globulin (SHBG). Approximately 2% of the testosterone exists in the free (unbound) forms which are the biologically active. Approximately 60% is tightly bound to SHBG. The resting testosterone is weakly bound to albumin and other proteins [6-8].

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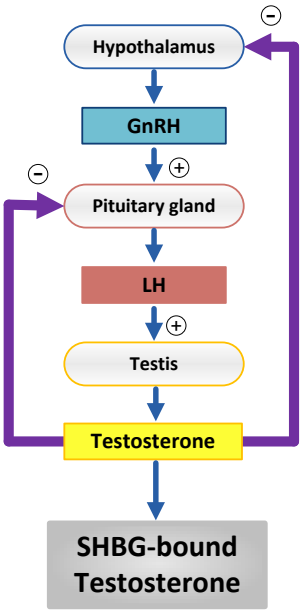

Fig. 1: The normal regulation of the hypothalamus down to the testis in the negative feedback mechanism. Hypothamic hormone (GnRH) secreted in plusatile pattern by the hypothalamus triggers the production of LH in pituitary gland. After LH is released to the bloodstream, it travels to the testis for stimulation of the testosterone secretion. The testosterone in turn acts to modulate GnRH and LH secretion by negative feedback

Mathematical models of the male sex hormone regulation have been numerously present and continuously developed over the decades. The classical model of testosterone regulation in the male is proposed by Smith [9]. The model is formed by the following differential equations

$$\begin{aligned} \dot{R} &= f(T) - b_1(R) , \\ \dot{L} &= g_1(R) - b_2(L) , \\ \dot{T} &= g_2(L) - b_3(T) . \end{aligned} \tag{1}$$

Where R, L and T are concentrations of GnRH, LH and Testosterone, respectively. The positive function b_1, b_2, b_3 refer to clearing rates of the hormones and g_1, g_2, f describe the hormone secretion rates, where b_1, b_2, b_3, g_1 and g_2 are the monotonic increasing functions and the negative feedback function f is a monotonic decreasing function. In 1983, Smith [10] improved the model in [9], he considered a period for LH hormone traveling from pituitary grand in the brain to the Leydig cells in the testis. In 1986, Cartwright and Husain [11] presented another model in order to account into the pulsatile release of the hormones within the HPG-axis, which is able to elucidate the cyclic behavior of GnRH and LH after castration. Greenhalgh and Khan [12] modified the models of Smith [10] and of Cartwright and Husain by using different response functions which incorporated more qualitatively observed biological behaviors. Tanutpanit et al. [13] extended a modified model in [12] to explain the presence of two types of testosterone hormones related with hypothalamic-pituitary-gonadal axis.

2. Mathematical Model

In this present work, the model considered in [13] is re-examined to interpret the relation of two forms of testosterone in the male hormonal regulation. Here, we need to introduce four variables; G for the plasma concentration of the gonadotropin-releasing hormone, Lh for the luteinizing hormone, Te for free testosterone and Ts for SHBG bound testosterone. We consider the change in SHBG-bound testosterone concentration is independent of itself. The model in this case can be expressed as

$$\begin{aligned}
\frac{dG}{dt} &= \frac{g_1 G}{Lh + g_2 Te} - m_1 G \ , \\
\frac{dLh}{dt} &= \left(\frac{k_1 G}{G + k_2 T}\right) Lh - m_2 Lh \ , \\
\frac{dTe}{dt} &= b \cdot Lh(t-\tau) \cdot Te + \left(\frac{k_3}{1 + k_4 \cdot Ts}\right) \cdot Te - m_3 T \ , \\
\frac{dTs}{dt} &= \frac{v_1 Te}{1 + v_2 Te} - m_4 Ts \ .
\end{aligned} \tag{2}$$

where $g_1, g_2, k_1, k_2, k_3, k_4, v_1, v_2$ and b are strictly positive parameters and m_1, m_2, m_3 and m_4 are defined as the metabolic clearance rates of all four hormones. We find that the above equations accord with the nonzero steady state $\bar{E}(\bar{G}, \overline{Lh}, \overline{Te}, \overline{Ts})$ where

$$\bar{G} = \frac{k_2 m_2}{k_1 - m_2} \overline{Te} \ , \quad \overline{Lh} = \frac{g_1}{m_1} - g_2 \overline{Te} \quad \text{and} \quad \overline{Ts} = \frac{v_1}{m_4}\left(\frac{\overline{Te}}{1 + v_2 \overline{Te}}\right)$$

And $\overline{Te}$ is the positive root of the quadratic equation

$$a \cdot Te^2 + b \cdot Te + c = 0$$

where

$$a = g_2 v_2 + \frac{g_2 k_4 v_1}{m_4}, \quad b = g_2 + \left(\frac{m_3}{b} - \frac{g_1}{m_1}\right)\left(v_2 + \frac{v_1 k_4}{m_4}\right) - \frac{v_2 k_3}{b} \quad \text{and} \quad c = \frac{m_1 m_3 - g_1 b - m_1 k_3}{m_1 b} \ .$$

Furthermore, because of the small change of SHBG-bound testosterone level in time[10], we such consider Ts as being in a quasi-steady-state. We invoke the steady-state approximation by setting $\frac{dTs}{dt}$ approximately equal to zero. Thus, from Ts -equation in (2) we have

$$Ts = \frac{1}{m_4}\left(\frac{v_1 Te}{1 + v_2 Te}\right) \tag{3}$$

Substituting it into eqs (2), then eqs. (2) reduces to

$$\begin{aligned}
\frac{dG}{dt} &= \frac{g_1 G}{Lh + g_2 Te} - m_1 G \ , \\
\frac{dLh}{dt} &= \left(\frac{k_1 G}{G + k_2 T}\right) Lh - m_2 Lh \ , \\
\frac{dTe}{dt} &= b \cdot Lh(t-\tau) \cdot Te + k_3 \left(\frac{1 + v_2 Te}{1 + \left(v_2 + \frac{k_4}{m_4} v_1\right) Te}\right) \cdot Te - m_3 T \ .
\end{aligned} \tag{4}$$

3. Numerical Results

Numerical simulations of the delayed system (4) are performed to exhibit the dynamical behavior depending on the delay parameter. We determine some parameter values like as in the simulation of Greenhalgh and Khan. Also, we give $v_1 = 1.5$/min, $v_2 = 0.08$/min, $k_4 = 1.47$/min and $m_4 = 0.0491$/min, which are estimated from the steady-state equation.

We used routine dde23 in MATLAB to simulate the behaviors for equation (4). Fig.2 shows the simulated results of GnRH, LH and testosterone which correspond to the steady state $\overline{E}$ that exhibits stable behavior where $\tau = 120$. Numerical simulations of the concentrations of the hormones in the system where $\tau = 125$, such varied behaviors occur in the form of periodic fluctuations, is shown in Fig.3.

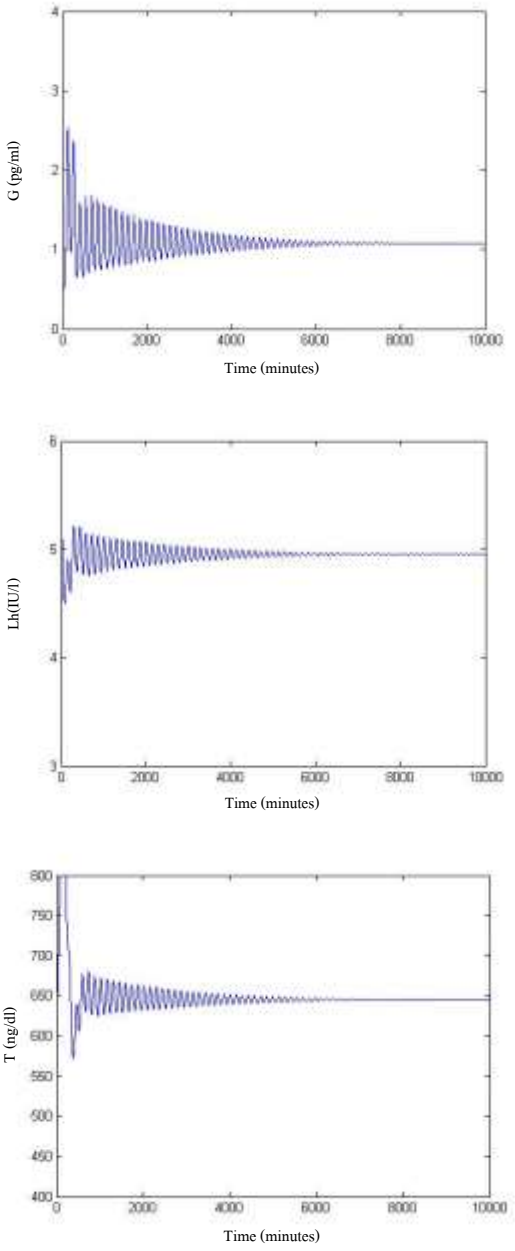

Fig. 2: The graphs show results of numerical simulations of hormone concentration $G(t)$ vs. time, $Lh(t)$ vs. time and $Te(t)$ vs. time for eqs.(4) with $\tau = 120$. Initial values are $(G_0, Lh_0, Te_0) = (1, 5.3, 600)$. The positive equilibrium is asymptotically stable.

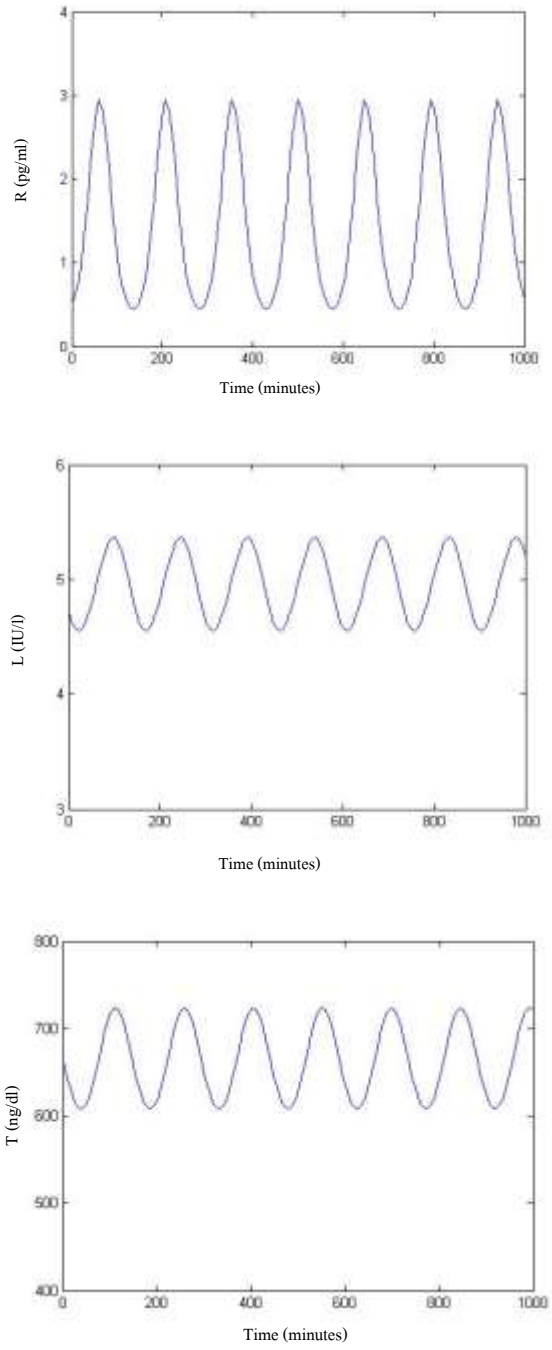

Fig. 3: The graphs show results of numerical simulations of hormone concentration $G(t)$ vs. time, $Lh(t)$ vs. time and $Te(t)$ vs. time for eqs.(4) with $\tau = 125$. Initial values are $(G_0, Lh_0, Te_0) = (1, 5.3, 600)$. The system exhibit periodic oscillations

4. Conclusion

We have modified the mathematical model of the male sex hormone regulation which explains a significant reaction between the two forms of testosterone within the hypothamic-pituitary-gonadal system. A time-delay which is corresponding to the LH secretion in the pituitary gland and travel of the hormone to the testis is considered in the model. It exhibits periodical solutions of the hormones that are consistent with the experimental data well.

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