Mathematical Biosciences 249 (2014) 1–7

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

A novel minimal mathematical model of the hypothalamus–pituitary–thyroid axis validated for individualized clinical applications

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ARTICLE INFO

Article history:
Received 14 October 2013
Received in revised form 7 January 2014
Accepted 9 January 2014
Available online 28 January 2014

Keywords:
Negative exponential
Parameterization
Individualized therapeutic target
Logarithmic–linear relationship
Clinical validation

ABSTRACT

The hypothalamus–pituitary–thyroid (HPT) axis represents a complex, non-linear thyroid hormone system in vertebrates governed by numerous variables. The common modeling approach until now aims at a comprehensive inclusion of all known physiological influences. In contrast, we develop a parsimonious mathematical model that integrates the hypothalamus–pituitary (HP) complex as an endocrinologic unit based on a parameterized negative exponential function between free thyroxine (FT4) as stimulus and thyrotropin (thyroid stimulating hormone, TSH) as response. Model validation with clinical data obtained from geographically different hospitals revealed a goodness-of-fit largely ranging between $90\% < R^2 < 99\%$, each HP characteristic curve being uniquely defined for each individual akin to a fingerprint. Specifically, the HP model represents the afferent feedback limb of the HPT axis while the efferent limb is mathematically depicted by TSH input to the thyroid gland which responds by secreting T4 as its chief output. The complete HPT axis thus forms a closed loop system with negative feedback resulting in an equilibrium state or homeostasis under defined conditions illustrated by the intersection of the HP and thyroid response characteristics. In this treatise, we demonstrate how this mathematical approach facilitates homeostatic set points computation for personalized dosing of thyroid medications of patients to individualized euthyroid states.

1. Introduction

As we enter into this present era of personalized medicine, there has never been a greater need for an individualized model governing the [FT4]–[TSH] relationship [1,2]. This is supported by an increasingly recognized observation that the wellbeing of many patients remains suboptimal despite having achieved "euthyroidism" defined by thyroid function within the normal population ranges of [FT4] and [TSH] [3].

For the purposes of this modeling strategy, we consider the hypothalamus–pituitary (HP) complex as one master regulator unit, calibrating its thyrotropin ([TSH]) response as a function of circulating free thyroxine ([FT4]). In order to elicit purely the properties of the HP response, we analyze the HP function in an open loop situation independent of the simultaneous confounding influence of the thyroid.

Although triiodothyronine [T3] is the main active hormone, the response characteristics analysis will be confined to the relationship between [FT4] and [TSH] [4]. This is valid as [TSH] is determined by the negative feedback action of the summation of [FT3] and [FT4] combined. Using a model with two degrees of freedom allows the contributory factor exerted by [FT3] to be completely subsumed within the two structural parameters such that only [FT4] remains the stimulus variable connecting [TSH] as the response.

Provided that the hypothalamus and pituitary are normal and not influenced by drugs or diseases, [TSH] varies inversely with [FT4] in a non-linear fashion whereby small changes in [FT4] can lead to fold-changes in [TSH] over several orders of magnitude [5,6]. When the [TSH] axis is presented using a linear scale, the non-linear inverse characteristic between [TSH] and [FT4] is apparent and resembles a hyperbolic, sigmoid or exponential decay function which motivated the development of the log-linear

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http://dx.doi.org/10.1016/j.mbs.2014.01.001
0025-5564/

standard model of thyroid homeostasis more than 40 years ago [5,6]. Interestingly, the normal reference interval of [TSH] and [FT4] values falls within the "knee" region of the HP curve encompassing the greatest curvature (i.e. minimum radius of curvature) on such a graphical plot. The HP characteristic thus contains a set of possible points of homeostasis over a certain range of [FT4] and [TSH] in which the normal [TSH]–[FT4] homeostatic euthyroid set point is coincidentally also found here, suggesting an evolutionary survival advantage conferred by nature for organisms to respond and calibrate their [TSH] output robustly to achieve tight homeostasis of their [FT4] levels within a narrow physiological window [7].

Recently, a modeling example of the [TSH]–[FT4] relationship [8] succeeded to constitute the well-known standard logarithmic model from a fundamental mathematical basis. The logarithmic model of thyrotropic HP response is consistent with existing data in the literature which show that this relationship is generally depicted graphically by the [TSH] axis plotted on a logarithmic scale and the [FT4] axis plotted on a linear scale. Such a log-linear plot still shows a hyperbolic or logistic decline curve that may be approximated by a straight line with a negative gradient using semi-log scales on a Cartesian grid [8]. As such, [TSH] may be expressed as a negative exponential function of [FT4]. Based on these fundamental considerations, we devise an *a priori* negative exponential asymptotic model with two independent model parameters. The validation of the model is based on individual [FT4]–[TSH] measurements (observation space), related mode selection and belonging model identification [9].

According to non-linear curve fitting algorithm from Johansen [10] the validation results of the model are presented. In order to illustrate the derivation of euthyroid homeostasis, we introduce a thyroid hormone secretion model [11] with parameterized secretory rates such that area of homeostasis is found from the intersection of the thyroid curves with the HP curves.

2. Modeling strategy

Many HPT axis models are based on physiological measurements and observations containing numerous model parameters that finally will result in a modeling representation [12–16] based on coupled differential equations. Because only a limited set of physiological characterizations can be observed, most other relevant factors on HPT dynamics and homeostasis cannot be included for practical use. Except for DiStefano et al. [14], none of the models were validated on individual cases. All models were hampered by a set of unknown physiological parameters that could not translate into individualized applications. Also the use of simulations cannot replace real and specific patients. In the same vein, statistical modeling generates results that poorly reflect actual physiology and are also irrelevant at the individual level. The introduction of perturbation and statistical methods is an attempt to adapt the model to noisy data and/or imprecise measurements. In the final analysis, a physiologically accurate model is best constructed by reliable and reproducible thyroid function tests (TFT) (i.e. [TSH]–[FT4] paired data) [17,18].

With this knowledge, we only use the integral effects of the HPT homeostatic response from individual [FT4] and [TSH] measurements. This approach delivers a successful and applicable model, verified by individual series of TFT to construct the individual HP characteristic.

The model has two degrees of freedom, respectively S (the multiplier) and φ (the slope of the exponential coefficient) as shown:

$$[\mathrm{TSH}] = S\exp(-\varphi[\mathrm{FT4}]) \tag{1}$$

In the following, the implications and consequences of various choices for all parameters involved will be discussed. The factor S, a linear component of the thyrotropic system, is related to the [FT4] range. Variation of S, with a fixed value for φ, horizontally translates the HP characteristic curve along the [FT4] axis as shown in Fig. 1.

When φ is fixed, we can appreciate from the first derivative of (1) to [TSH]

$$\frac{d[\mathrm{TSH}]}{d[\mathrm{FT4}]} = -\varphi S\exp(-\varphi[\mathrm{FT4}]) = -\varphi[\mathrm{TSH}] \tag{2}$$

This implies that the first derivative will not change at fixed φ with variation of S.

When φ assumes a fixed known value, the value of S may be inferred from different [FT4]–[TSH] coordinates as given by:

$$S = [\mathrm{TSH}]\exp(\varphi[\mathrm{FT4}]) \tag{3}$$

The second model parameter φ represents the exponential factor. Variation of φ folds or unfolds the shape of the HP characteristic centered on a chosen set of coordinates. Notably, φ and S are inter-related accordingly to any [FT4]–[TSH] coordinate on the HP characteristic:

$$\varphi = \left(\frac{1}{[\mathrm{FT4}]}\right)\ln\left(\frac{S}{[\mathrm{TSH}]}\right) \tag{4}$$

In Fig. 2, the folding effect of the variation of φ is shown, while the HP curves 'rotate' around a defined point P.

Figs. 1 and 2 depict the theoretical range of values that φ and S can possibly assume under most clinical circumstances. Additionally, φ and S always form a parameter set describing a specific curve for a specific person. From Eq. (2), it can be readily appreciated that the first derivatives at the intersecting point, P, are only dependent on the value of φ.

Evidently, in general, a single point measured in the [FT4]–[TSH] plane cannot be used to generate a valid characteristic of the HP. Exponential functions have the property that such a function is completely defined by two different coordinates. With a set of at least two [FT4]–[TSH] measurements of a single person in the process of treatment for hypothyroidism or hyperthyroidism, measured over an interval of several weeks, the characteristic is completely determined by solving the simultaneous equations for the model parameters S and φ, provided that the thyroid function test results are not repeatedly identical and the effect of hysteresis is negligible. Based on these considerations, it is possible to obtain a reliable calculation of the HP function from [FT4] to [TSH] pairs obtained during changing treatment conditions in an open-loop situation [17].

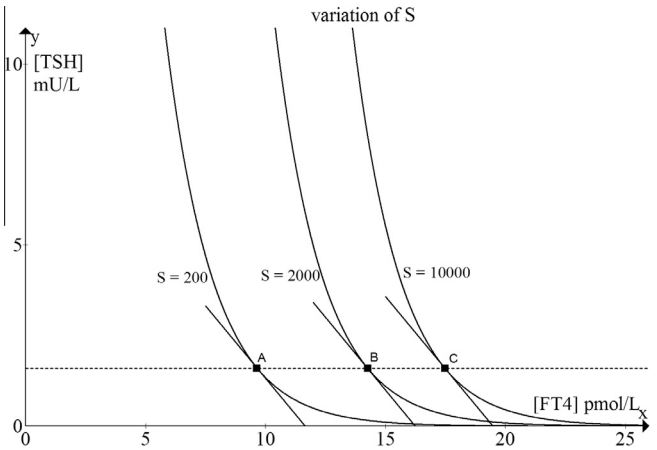

Fig. 1. Shifting the HP curve along the [FT4] axis as a function of S with a fixed value for φ. The values of S, $200 < S < 10{,}000$ are here only used as an example in practice S can be as small as 10 and in the higher regions can reach values of 10E+6.