Journal of Theoretical Biology 321 (2013) 8–27

Contents lists available at SciVerse ScienceDirect

Journal of Theoretical Biology

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

A mathematical model of the human menstrual cycle for the administration of GnRH analogues

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HIGHLIGHTS

- Menstrual cycle feedback mechanisms are described using differential equations.
- GnRH, FSH, LH, E2, P4, inhibins A and B, and follicular development are modeled.
- The model predicts hormonal changes following GnRH analogue administration.
- Simulation results agree with measurements of hormone blood concentrations.
- The model gives insight into mechanisms underlying gonadotropin suppression.

ARTICLE INFO

Article history:
Received 2 March 2012
Received in revised form
27 September 2012
Accepted 19 November 2012
Available online 1 December 2012

Keywords:
Endocrinology
Reproduction
Hormone secretion
Systems pharmacology
Periodic behavior

ABSTRACT

The paper presents a differential equation model for the feedback mechanisms between gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), development of follicles and corpus luteum, and the production of estradiol (E2), progesterone (P4), inhibin A (IhA), and inhibin B (IhB) during the female menstrual cycle. Compared to earlier human cycle models, there are three important differences: The model presented here (a) does not involve any delay equations, (b) is based on a deterministic modeling of the GnRH pulse pattern, and (c) contains less differential equations and less parameters. These differences allow for a faster simulation and parameter identification. The focus is on modeling GnRH-receptor binding, in particular, by inclusion of a pharmacokinetic/pharmacodynamic (PK/PD) model for a GnRH agonist, Nafarelin, and a GnRH antagonist, Cetrorelix, into the menstrual cycle model. The final mathematical model describes the hormone profiles (LH, FSH, P4, E2) throughout the menstrual cycle of 12 healthy women. It correctly predicts hormonal changes following single and multiple dose administration of Nafarelin or Cetrorelix at different stages in the cycle.

1. Introduction

GnRH plays an important role in the female menstrual cycle (Neill, 2006). It controls the complex process of follicular growth, ovulation, and corpus luteum development. GnRH is responsible for the synthesis and release of the gonadotropins FSH and LH from the anterior pituitary to the blood (Hall, 2009). These processes are controlled by the size and frequency of GnRH pulses. In males, the GnRH pulse frequency is constant, but in females, the frequency varies during the menstrual cycle, with a large surge of GnRH just before ovulation. Low-frequency pulses lead to FSH release, whereas high frequency pulses stimulate LH release (Marshall and Griffin, 1993). Thus, pulsatile GnRH secretion is necessary for correct reproductive function. Since GnRH itself is of limited clinical use due to its short life-span, modifications around its lead structure have led to GnRH *analogues* whose overall aim is to suppress the gonadotropins (Engel and Schally, 2007).

There are two types of GnRH analogues: agonists and antagonists. GnRH *agonists* act just like natural GnRH, resulting in an

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http://dx.doi.org/10.1016/j.jtbi.2012.11.020

initial increase in FSH and LH secretion ("flare effect"). After their initial stimulating action, agonists are able to exert a prolonged suppression effect on the receptors, termed "down-regulation" or "desensitization", which can be observed after about 10 days (vanLoenen et al., 2002). Usually, this induced and reversible hypogonadism is the therapeutic goal. GnRH agonists are used, for example, for the treatment of cancer, endometriosis, uterine fibroids, and precocious puberty, as well as for in vitro fertilization (IVF) (Engel and Schally, 2007). GnRH *antagonists* compete with natural GnRH for binding to GnRH receptors, but the antagonist–receptor complex has no effect on the gonadotropins. Thus, antagonists lead to an acute suppression of the hypothalamic–pituitary–gonadal (HPG) axis without an initial gonadotropin surge. Today, GnRH antagonists are mainly used in IVF treatment to block natural ovulation (Cetrorelix, Ganorelix) and in the treatment of prostate cancer (Abarelix, Degarelix) (Engel and Schally, 2007). For several reasons, such as high dosage requirements and the incidence of allergies at an early stage of drug development, the commercialization of GnRH antagonists lagged behind their agonist counterparts (Garnick, 2001). Therefore, GnRH agonists became more popular in IVF treatment, even though antagonist treatment is easier to conduct (shorter treatment period, reduced risk for ovarian hyperstimulation syndrome) and reproductive outcomes are comparable (Griesinger and Diedrich, 2007).

The aim of the present paper is to develop a mathematical model that characterizes the actions of GnRH agonists and antagonists by their different effects on the HPG axis. The model should be able to explain blood concentrations of LH, FSH, E2, and P4 after single and multiple dose treatment with a GnRH analogue during different stages of the menstrual cycle, as reported in Duijkers et al. (1998), Leroy et al. (1994), Monroe et al. (1985) and Monroe et al. (1986). Such a model should eventually help in preparing and monitoring clinical trials with new drugs that affect GnRH receptors, as well as in the selection of new targets in this pathway. We thus aim at contributing to the newly emerging discipline of quantitative and systems pharmacology (QSP) (Ward, 2011), which combines systems biology and pharmacology in academia and industry in order to enhance drug discovery and development (van der Graaf, 2012).

Since data are available only for some model features, we follow a semi-mechanistic modeling approach, in which mechanistic aspects of physiologic processes, e.g. feedback loops along the HPG axis, are combined with some heuristic features, e.g. follicular stages of maturation. Hill functions are used to model qualitative features such as inhibitory or stimulatory effects.

Although comprising several organs (hypothalamus, pituitary, blood, ovaries), the model presented here does not take into account signal transduction on a cellular level. Bridging the gap between multiple scales in space and time is definitely a challenging task on the biological modeling agenda. The authors do hope that making our mathematical tools accessible to a general audience will support this process.

Nevertheless, the purpose of the present paper is to provide a starting point for an incremental model development in terms of equations and parameter values for the human menstrual cycle. We hope that other researchers will be enabled to refine the presented model, once new approaches for incorporating processes at several temporal and spatial scales are available.

There already exist PK/PD models for GnRH analogues (Nagaraja et al., 2003; Tornøe et al., 2006; Jadhav et al., 2006). These models describe the influence on LH and/or FSH but do not include GnRH receptor binding mechanisms. Our goal is to merge such a PK/PD model via detailed GnRH receptor binding mechanisms with a large kinetic model of the fully coupled feedback mechanisms in the human menstrual cycle. At present, there are only few publications available that focus on these feedback mechanisms. In 1999, a differential equation model that contains the regulation of LH and FSH synthesis, release, and clearance by E2, P4, and Ih was introduced by Selgrade and Schlosser (1999) and Schlosser and Selgrade (2000). This model was extended by Selgrade (2001), Harris (2001), Harris Clark et al. (2003) and later by Pasteur (2008) to describe the roles of LH and FSH during the development of ovarian follicles and the production of the ovarian hormones E2, P4, IhA, and IhB. Reinecke and Deuflhard (2007) and Reinecke (2009) added, among other things, a stochastic GnRH pulse generator and GnRH receptor binding mechanisms.

Parametrization of the model in Reinecke and Deuflhard (2007) and Reinecke (2009) was based on averaged data for LH, FSH, E2, and P4 throughout one normal cycle. Our first goal was to check whether that model was capable of predicting a situation that had not been used to parametrize it, namely the administration of GnRH analogues. Unfortunately, its predictive capacity turned out to be limited. Simulations of GnRH analogue treatments via the existing GnRH equations were unable to adequately describe the decrease in free GnRH receptors following single agonist doses. Moreover, the menstrual cycle did not return to its initial state at the beginning of the next cycle. In addition, the pulsatile pattern of GnRH required extremely small computational timesteps which led to intolerable simulation times. Simply re-parameterizing the model did not improve the results because mechanistic details essential for our new aims were missing. Hence, re-parametrization had to be accompanied by both model reduction and model refinement to explain the new experimental data from GnRH analogue treatments, while maintaining the fit to former normal cycle data. The results of this intensive collaboration over years are presented here.

The paper is organized as follows. In Section 2 we derive the model equations with special focus on GnRH receptor binding and the coupling to a PK model. Simulation results for the normal cycle as well as for the treatment with Nafarelin and Cetrorelix are presented and discussed in Section 3. The conclusion follows in Section 4. Details on data sources, initial values and parameter values as well as consistency of units are postponed to an appendix.

2. Model equations

A qualitative description of the model to be presented is illustrated as a flowchart in Fig. 1. In the hypothalamus, the hormone GnRH is formed, which reaches the pituitary gland through the portal system and stimulates the release of the gonadotropins LH and FSH into the bloodstream. These gonadotropins regulate the processes in the ovaries, i.e. the multi-stage maturation process of the follicles, ovulation and the development of the corpus luteum, which control the synthesis of the steroids P4 and E2 and of the hormones IhA and IhB. Through the blood, these hormones then reach the hypothalamus and pituitary gland, where they again influence the formation of GnRH, LH and FSH. All model components are listed in Table 1. Except *freq* and *mass*, which are described by algebraic expressions,[1] all components are defined by differential equations.

Since exact mechanisms are often unknown or just too complex, Hill functions are used to model stimulatory (H^+) or inhibitory (H^-) effects:

$$H^+(S(t),T;n)=\frac{(S(t)/T)^n}{1+(S(t)/T)^n},\quad H^-(S(t),T;n)=\frac{1}{1+(S(t)/T)^n}$$

[1] In the Systems Biology Markup Language (SBML), they are defined by assignment rules.