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

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

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Abstract

This study 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. In contrast to other models, this model does not involve delay differential equations and is based on deterministic modelling of the GnRH pulse pattern, which allows for faster simulation times and efficient parameter identification. These steps were essential to tackle the task of developing a mathematical model for the administration of GnRH analogues. The focus of this paper is on model development for GnRH receptor binding and the integration of a pharmacokinetic/pharmacodynamic model for the GnRH agonist Nafarelin and the GnRH antagonist Cetrorelix into the menstrual cycle model. The final mathematical model describes the hormone profiles (LH, FSH, P4, E2) throughout the menstrual cycle in 12 healthy women. Moreover, it correctly predicts the changes in the cycle following single and multiple dose administration of Nafarelin or Cetrorelix at different stages in the cycle.

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1 Introduction

The gonadotropin-releasing hormone (GnRH) plays an important role in the female reproductive cycle. GnRH controls the complex process of follicular growth, ovulation, and corpus luteum development. It is responsible for the synthesis and release of gonadotropins (follicle-stimulating hormone (FSH) and luteinizing hormone (LH)) from the anterior pituitary to the blood. 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. Thus, pulsatile GnRH secretion is necessary for correct reproductive function.

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Since GnRH itself is of limited clinical use due to its short half-life, modifications of its structure have led to GnRH analog medications that either stimulate (GnRH agonists) or suppress (GnRH antagonists) the gonadotropins. Agonists do not quickly dissociate from the GnRH receptor, resulting in an initial increase in FSH and LH secretion ("flare effect"). After their initial stimulating action, agonists are able to exert a prolonged suppression effect , termed "downregulation" or "desensitization", which can be observed after about 10 days. Generally 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 [10].

GnRH antagonists compete with natural GnRH for binding to GnRH receptors, thus leading to an acute suppression of the hypothalamic-pituitary-gonadal axis without an initial surge. For several reasons, such as high dosage requirements, the commercialization of GnRH antagonists lagged behind their agonist counterparts [12]. Today, GnRH antagonists are mainly used in IVF treatment to block natural ovulation (Cetrorelix, Ganorelix) and in the treatment of prostate cancer (Abarelix, Degarelix) [10].

The fundamental understanding of the receptor response is necessary to create safer pharmaceutical drugs. Therefore, the aim of this paper is to develop a mathematical model that characterizes the different actions of GnRH agonists and antagonists by their different effects on the GnRH receptor binding mechanisms. The model should be able to explain measurement values for the blood concentrations of LH, FSH, estradiol (E2), and progesterone (P4) after single and multiple dose treatment with a GnRH agonist or antagonist. Such a model should eventually help in preparing and monitoring clinical trials with new drugs that affect GnRH receptors.

There are only a few publications available that focus on feedback mechanisms in the female menstrual cycle. In 1999, a differential equation model that contains the regulation of LH and FSH synthesis, release, and clearance by E2, P4, and inhibin was introduced by Schlosser and Selgrade [36, 33]. This model was extended by Selgrade [35], Harris [16, 17] and later by Pasteur [30] to describe the roles of LH and FSH during the development of ovarian follicles and the production of the ovarian hormones E2, P4, inhibin A (IhA), and inhibin B (IhB). Reinecke and Deuflhard [32, 31] added, among other things, a stochastic GnRH pulse generator and GnRH receptor binding mechanisms. This model was insufficient for our purpose and needed modifications.

On the other hand, there exist pharmacokinetic/pharmacodynamic (PK/PD) models for GnRH analogues [28, 38, 20]. These models describe the influence on LH and/or FSH but do not include the GnRH receptor binding mechanisms. Our goal is to couple such a PK/PD model with the model of the female menstrual cycle.

The paper is organized as follows. In Sec. 2 we derive the model equations with special focus on the GnRH receptor binding model and the coupling of a PK model. The problem of parameter identification is addressed in Sec. 3. Sec. 4 contains the simulation results for the normal cycle as well as for the treatment with Nafarelin and Cetrorelix. The conclusion follows in Sec. 5. Details about initial values and parameter values as well as a list of abbreviations are shifted to the appendix.

2 Model Equations

The model of the female menstrual cycle includes the physiological compartments hypothalamus, pituitary gland and ovaries, connected by the bloodstream. The model delivers a qualitative description of the following regulatory circuit as illustrated in the flowchart in Fig. 1: In the hypothalamus, the hormone GnRH (gonadotropin-releasing hormone) is formed, which reaches the pituitary gland through a portal system and stimulates the release of the gonadotropins LH and FSH into the bloodstream. The 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.

Since exact mechanisms are often unknown or more specific than necessary, Hill functions are

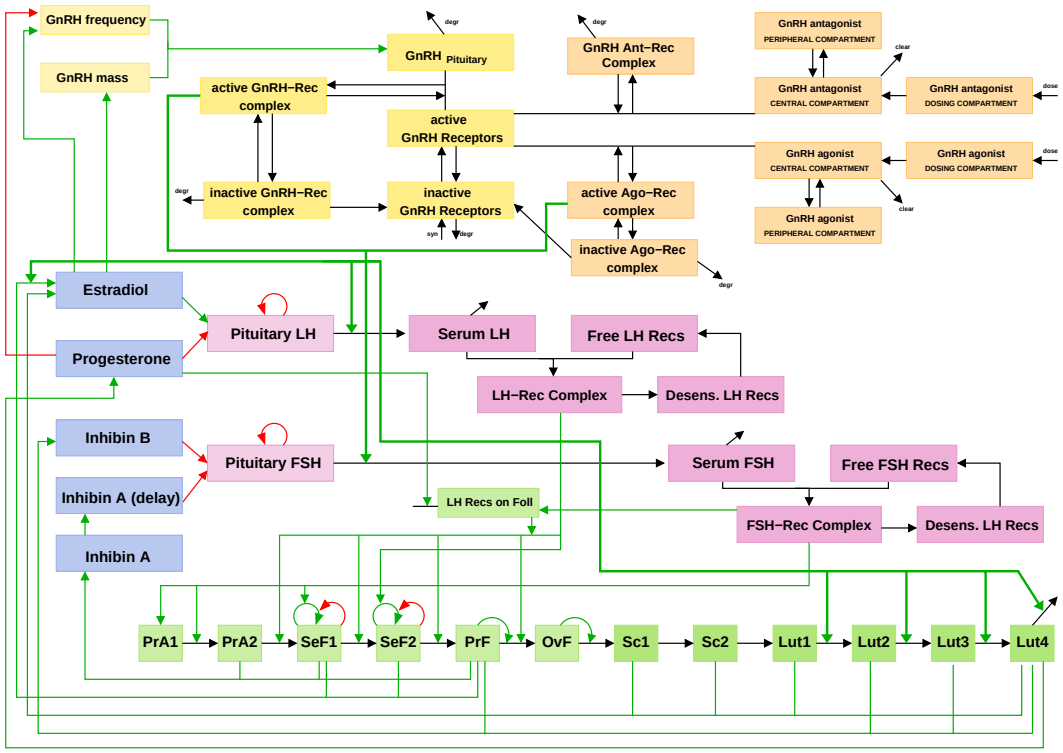

Figure 1: Flowchart of the model for the female menstrual cycle.

used to model stimulatory (H^+) or inhibitory (H^-) effects:

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

Here, $S(t) \geq 0$ denotes the influencing substance, $T > 0$ the threshold, and $n \geq 1$ the Hill coefficient, which determines the rate of switching.

The following model equations partially overlap with equations used in the models of Harris [16], Pasteur [30] and Reinecke [31], but have been extended and adapted for the purpose of simulating GnRH analogue treatment. We started with the Reinecke model (named "original" model) and performed model extension and reduction. First, we reduced this model by omitting components which couple only weakly to the rest of the model. In particular, we left out the enzyme reactions in the ovaries. According to [30], the number of follicular phases was extended from 5 to 8 in order to distinguish between IhA and IhB. Moreover, we replaced the stochastic GnRH pulse generator by a deterministic counterpart, which will be explained in more detail in Sec. 2.5.

2.1 Luteinizing Hormone

The gonadotropin equations are based on synthesis-release-clearance relationships. This structure was first introduced in [33]. LH-synthesis in the pituitary is stimulated by E2 and inhibited by P4. There is a small constant release rate of LH into the blood ($b_{\mathrm{LH}_{Rel}}$) [19], but the release is mainly stimulated by the GnRH-receptor complex and additionally, if present, by the agonist-receptor complex. Parameter V_{blood} corresponds to the blood volume. From the blood, LH is cleared by