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MINI-REVIEW

Novel aspects of the endocrinology of the menstrual cycle

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Abstract Ovarian control of gonadotrophin secretion is normally achieved via the feedback mechanisms mediated by oestradiol and progesterone. Evidence has been provided that nonsteroidal substances, such as inhibin A and B, participate in the negative feedback control of FSH secretion. Another nonsteroidal ovarian substance is gonadotrophin surge-attenuating factor (GnSAF), the activity of which is particularly evident in women undergoing ovulation induction. Accumulating evidence has suggested that GnSAF plays a physiological role during the menstrual cycle. In particular, this factor antagonizes the sensitizing effect of oestradiol on the pituitary response to gonadotrophin-releasing hormone during the follicular phase of the cycle. A hypothesis has been developed that, in the late follicular phase, the activity of GnSAF is reduced and this facilitates the sensitizing effect of oestradiol on the pituitary, thus enforcing the massive discharge of gonadotrophins at the midcycle LH surge. The interaction of oestradiol, progesterone and GnSAF on the hypothalamic–pituitary system provides a novel approach to explain the mechanisms which control LH secretion during the normal menstrual cycle.

KEYWORDS: GnSAF, gonadotrophins, inhibin, oestradiol, ovary, progesterone

Introduction

The human menstrual cycle is characterized by a cyclic pattern of hormonal changes which are regulated by the feedback mechanisms. Ovarian hormones, either steroids or nonsteroidal in nature, are the main mediators of the ovarian effects on the hypothalamic–pituitary system. Marked changes, particularly during negative feedback, take place throughout life: this mode of ovarian control of gonadotrophin secretion is very potent in the early years of life, but is almost eliminated after menopause (Messinis, 2006a).

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It has been established that, during the menstrual cycle, ovarian steroids are the principal mediators of the feedback mechanisms (Messinis, 2006b). Recent evidence, however, has clarified more specific roles of these substances in the secretion of the two gonadotrophins from the pituitary. Regarding nonsteroidal substances secreted by the ovaries, their action in the context of the feedback mechanisms provides a novel approach to the understanding of the physiology of pituitary gonadotrophin secretion. Such substances include the two inhibins, A and B, and a factor named gonadotrophin surge-attenuating factor (GnSAF). The two principal steroids secreted by the ovaries are oestradiol, in the follicular phase, and progesterone, in the luteal phase. Nevertheless, the role of each is not confined to certain stages of the menstrual cycle, and they are important regulators of gonadotrophin secretion throughout the whole cycle. For example, progesterone, although at low concentration, is also present in the circulation during the follicular phase of the cycle and a physiological endocrine role for this steroid has been further examined (Dafopoulos et al., 2004).

In this review, the contribution of steroidal and nonsteroidal ovarian substances in the regulation of gonadotrophin secretion in women during the menstrual cycle, particularly in the follicular phase and at midcycle, will be discussed taking into consideration conventional knowledge and recent information.

Follicular phase

It is known that oestradiol is the main secretory product of the follicle during the follicular phase of the cycle and is the principal ligand binding to receptors to induce the negative feedback regulation in the hypothalamic–pituitary system. Several studies have thoroughly investigated ovarian negative feedback either in experiments involving the exogenous administration of ovarian steroids or after the increased production of endogenous oestrogens during ovarian stimulation with FSH (Messinis, 2006b). Another approach to study the negative feedback mechanism is the elimination of endogenous ovarian hormones, such as after ovariectomy or after inactivation by the administration of selective oestrogen receptor modulators (Alexandris et al., 1997; Messinis and Templeton, 1988). That the exogenous oestrogens can suppress FSH and LH concentrations has been shown in several studies (Messinis and Templeton, 1990; Monroe et al., 1972; Tsai and Yen, 1971; Young and Jaffe, 1976).

In a more recent study, in which exogenous oestradiol and progesterone were given to healthy post-menopausal women in order to create 'simulated' follicular and luteal phases, it was found that with these steroids, LH decreased to a normal premenopausal concentration, while FSH concentration, although decreased, remained higher than during the normal early follicular phase (Dafopoulos et al., 2004). These results suggest that the two gonadotrophins are differentially controlled by the ovaries and that FSH secretion is also regulated by substances other than the steroids. Following the decrease in LH, exogenous oestradiol alone was unable to maintain LH concentration in the range seen in the early follicular phase, suggesting, that during the follicular phase of the natural cycle, ovarian substances in addition to oestradiol contribute to the control of LH secretion (Dafopoulos et al., 2004). Such a substance is likely to be progesterone, despite the blood concentration of this steroid being low during the follicular phase of the cycle.

Progesterone is produced by the ovaries not only in the luteal but also during the follicular phase of the cycle, since ovariectomy performed in women at that stage of the cycle resulted in a significant decrease in serum concentration of this steroid (Alexandris et al., 1997). Furthermore, treatment of women with the anti-progesterone, mifepristone, during the follicular phase of the cycle resulted in a significant increase in basal LH (Kazem et al., 1996). It is likely, therefore, that during the follicular phase of the cycle it is not only oestradiol but also progesterone that plays an important role in the control of LH secretion, in the context of the negative feedback mechanism.

Several studies have demonstrated that induction of multiple follicular development with the administration of exogenous FSH leads to a rapid increase in oestradiol to a supraphysiological concentration and a concomitant reduction in basal LH (Messinis and Templeton, 1987; Messinis et al., 1994, 1998). During the period of FSH administration and the concurrent increase in oestradiol concentration, serum progesterone remains low. These findings further support the role of oestradiol as the primary mediator of the negative feedback mechanism and that progesterone action is complementary to that of oestradiol. Further experiments in normally cycling women have demonstrated that during treatment with the anti-oestrogenic compound, clomiphene citrate, a gradual but significant rise in LH takes place, which lasts for the whole period of the administration of this drug, supporting thus the role of oestrogens in the negative control of gonadotrophin secretion (Messinis and Templeton, 1988).

Apart from the steroids, the ovaries also produce nonsteroidal substances, such as inhibin. By definition, inhibin is an ovarian substance that inhibits the secretion of FSH from the pituitary (Frachimont et al., 1975). It is known that inhibin B is secreted mainly by the growing antral follicles during the early follicular phase of the cycle, while inhibin A is secreted especially by the corpus luteum (Bicsak et al., 1986; De Kretser et al., 2002; Roberts et al., 1993). Measurements of these substances in blood have demonstrated that inhibin B concentration increases in the early follicular phase and declines thereafter until midcycle, where a peak is noted, while the concentration is low during the luteal phase (Groome et al., 1996). In contrast, inhibin A concentration is low in the follicular phase but increases markedly during the luteal phase of the cycle, and the pattern is similar to that of progesterone (Groome et al., 1996).

Regarding a physiological endocrine role of inhibin in the secretion of gonadotrophins, data have been derived mainly from experiments performed in animals. For example, the administration of inhibin anti-serum to rats and hamsters resulted in a significant increase in FSH-β mRNA without affecting LH-β mRNA (Attardi et al., 1992; Kishi et al., 1996). Furthermore, recombinant inhibin A given to rats or monkeys resulted in the blockage of the FSH surge and the suppression of plasma FSH (Rivier and Vale, 1991; Tilbrook et al., 1993). In addition, experiments in rhesus monkeys