HORMONAL REGULATION OF OVARIAN ACTIVITY

In contrast to the testis, the activities of the ovary occur in a cycle. Thus, the formation of follicles (including the growth of the ovum), ovulation, formation of the corpus luteum, and its regression all occur in appropriate order within a single monthly cycle. Similarly, the secretion of estrogen at first, followed by progesterone, from the follicle and corpus luteum takes place in a cyclical fashion. In this plate, we study how the operation of a hypothalamic "clock," along with intricate feedback effects of the ovarian hormones on the hypothalamus-anterior pituitary complex, ensures the orderly operation of the ovarian cycle.

PITUITARY GONADOTROPINS. The anterior pituitary secretes two hormones that regulate the activity of the ovary. These are the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH), collectively called gonadotropins. Both are glycoprotein molecules and are secreted from the basophilic gonadotropes. Both LH and FSH are necessary for all ovarian activity. In the follicular phase, FSH regulates follicular growth while LH stimulates estrogen secretion. LH, however, appears to be the predominant hormone, eliciting ovulation and growth of the corpus luteum as well as stimulation of progesterone and estrogen secretion by the corpus luteum.

HYPOTHALAMIC CONTROL. These pituitary gonadotropins are released in response to a signal from the hypothalamus in the form of a peptide neurohormone called the gonadotropin-releasing hormone (GnRH), released by the axon terminals of hypothalamic neurons into the portal hypophyseal capillaries, which deliver this substance rapidly and directly to the gonadotrope cells. There are receptors for GnRH on the surface of the gonadotropes. Recent research indicates that GnRH is released in pulses at hourly intervals. If increased release of gonadotropin is required, the amount of GnRH per pulse will be increased, and vice versa. It is not known how GnRH can differentially regulate LH and FSH secretions. In primates, levels of sex hormones can also influence LH and FSH secretions by direct effects on the pituitary. The pattern and amount of GnRH release is under the control of two mechanisms, a hypothalamic "clock" that sets the duration of the cycle and the timing of major events and the feedback effects of sex hormones on the hypothalamus and pituitary.

NEGATIVE AND POSITIVE FEEDBACK. Late in the ovarian cycle, when the endometrium is in the ischemic phase, preparing for menstruation, the very low level of estrogen acting via negative feedback stimulates the hypothalamus and pituitary. This causes increased output of GnRH, leading in turn to increased output of FSH and LH. These hormones stimulate follicular growth and increase estrogen output. By day 12 of the menstrual cycle, estrogen output is at its peak and FSH production has diminished due to the negative feedback inhibition by estrogen. The peak levels of estrogen will now act through a positive feedback system, increasing sensitivity of the pituitary to GnRH. This will cause a burst in the release of LH and FSH, but that of LH is many times higher and very crucial. The high levels of LH trigger the process of ovulation, which results, in several hours, in the expulsion of the ovum.

The postovulatory high levels of LH (and also of FSH) promote the secretion, mainly of progesterone and also of estrogen, by the corpus luteum cells. Gradually, the negative feedback effect will return. Thus, the increasing output of progesterone and estrogen will act on the hypothalamus and pituitary to diminish LH and FSH production. At the beginning of the fourth quarter of the ovarian cycle, progesterone and estrogen are at peak levels, and LH and FSH levels have fallen off. In the absence of fertilization, the low LH and FSH levels, as well as other factors such as locally produced prostaglandins, will cause the corpus luteum to lyse and regress, leading to diminished progesterone and estrogen output. This is the end of the cycle, and it is accompanied by menstruation. Gradually, the low levels of estrogen will relieve the inhibition over hypothalamic GnRH release, leading to increased FSH and LH output from the pituitary. This event will activate the second ovarian cycle. Illness, malnutrition, severe stress, and emotional crises interfere with the operation of the ovarian cycle. Stress and emotional crises act on the higher brain centers and, from there, on the hypothalamus, interfering with the pattern of GnRH release. Often the release is inhibited, leading to reduction in FSH and LH levels. Depending on the timing of the stress, diminished estrogen may cause undue menstruation (spotting) or delayed menstruation (secondary amenorrhea) due to the absence of endometrial proliferation.