Male and female sex hormones

Luteinizing hormone

(LH, also known as lutropin and sometimes lutrophin) is a hormone produced by gonadotroph cells in the anterior pituitary gland. In females, an acute rise of LH ("LH surge") triggers ovulation and development of the corpus luteum. In males, where LH had also been called interstitial cell-stimulating hormone (ICSH) it stimulates Leydig cell production of testosterone. It acts synergistically with FSH. LH is released from the pituitary gland, and is controlled by pulses of gonadotropin-releasing hormone (GnRH).

Structure

LH is a heterodimeric glycoprotein. Each monomeric unit is a glycoprotein molecule; one alpha and one beta subunit make the full, functional protein. Its structure is similar to that of the other glycoprotein hormones, follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and human chorionic gonadotropin (hCG). The protein dimer contains 2 glycopeptidic subunits, labeled alpha and beta subunits, that are non-covalently associated.

Activity

In females, LH supports theca cells in the ovaries that provide androgens and hormonal precursors for estradiol production. At the time of menstruation, FSH initiates follicular growth, specifically affecting granulosa cells. With the rise in estrogens, LH receptors are also expressed on the maturing follicle, which causes it to produce more estradiol. Eventually, when the follicle has fully matured, a spike in 17-hydroxyprogesterone production by the follicle inhibits the production of estrogen, leading to a decrease in
estrogen-mediated negative feedback of GnRH in the hypothalamus, which then stimulates the release of LH from the anterior pituitary. This increase in LH production only lasts for 24 to 48 hours. This "LH surge" triggers ovulation, thereby not only releasing the egg from the follicle, but also initiating the conversion of the residual follicle into a corpus luteum that, in turn, produces progesterone to prepare the endometrium for a possible implantation. LH is necessary to maintain luteal function for the first two weeks of the menstrual cycle. If pregnancy occurs, LH levels will decrease, and luteal function will instead be maintained by the action of hCG.

In males, LH acts upon the Leydig cells of the testis and is regulated by GnRH. The Leydig cells produce testosterone (T) under the control of LH, which regulates the expression of the enzyme 17-β hydroxysteroid dehydrogenase that is used to convert androstenedione, the hormone produced by the gonads, to testosterone, an androgen that exerts both endocrine activity and intra testicular activity on spermatogenesis. When testosterone levels are low, GnRH is released by the hypothalamus, stimulating the pituitary gland to release LH.[10] As the levels of testosterone increase, it will act on the hypothalamus and pituitary through a negative feedback loop and inhibit the release of GnRH and LH consequently. However, testosterone must first be aromatized into Estradiol (E2) in order to inhibit LH. E2 decreases pulse amplitude and responsiveness to GnRH from the hypothalamus onto the pituitary.

**Reference ranges for the blood content of luteinizing hormone (LH) during the menstrual cycle.**

The ranges denoted By biological stage may be used in closely monitored menstrual cycles in regard to other markers of its biological progression, with the time scale being
compressed or stretched to how much faster or slower, respectively, the cycle progresses compared to an average cycle. The ranges denoted Inter-cycle variability are more appropriate to use in non-monitored cycles with only the beginning of menstruation known, but where the woman accurately knows her average cycle lengths and time of ovulation, and that they are somewhat averagely regular, with the time scale being compressed or stretched to how much a woman's average cycle length is shorter or longer, respectively, than the average of the population. * The ranges denoted Inter-woman variability are more appropriate to use when the average cycle lengths and time of ovulation are unknown, but only the beginning of menstruation is given.

**Predicting ovulation**

The detection of a surge in release of luteinizing hormone indicates impending ovulation. LH can be detected by urinary ovulation predictor kits (OPK, also LH-kit) that are performed, typically daily, around the time ovulation may be expected.

A conversion from a negative to a positive reading would suggest that ovulation is about to occur within 24–48 hours, giving women two days to engage in sexual intercourse or
artificial insemination with the intentions of conceiving. Tests may be read manually using a color-change paper strip, or digitally with the assistance of reading electronics.

**FSH**

Follicle-stimulating hormone (FSH) is synthesized and secreted by gonadotrophs of the anterior pituitary gland. FSH regulates the development, growth, pubertal maturation and reproductive processes of the body. FSH and luteinizing hormone (LH) act synergistically in reproduction. FSH is a 35.5kD glycoprotein dimer. Its structure is similar to those of LH, thyroid-stimulating hormone (TSH) and, human chorionic gonadotropin (hCG, a hormone produced in pregnancy). The protein dimer contains 2 polypeptide units. The sugar part of the hormone is composed of fucose, galactose, mannose, galactosamine, glucosamine, and sialic acid, the latter being critical for its biologic half-life. The half-life of FSH is 3–4 hours.

**Activity**

FSH regulates the development, growth, pubertal maturation and reproductive processes of the human body. In both males and females, FSH stimulates the maturation of germ cells. In males, FSH induces Sertoli cells to secrete Androgen-binding proteins (ABPs) and its secretion is being regulated by inhibin's negative feedback mechanism on Anterior Pituitary gland.

In females, FSH initiates follicular growth, specifically affecting granulosa cells. With the concomitant rise in inhibin B, FSH levels then decline in the late follicular phase. This seems to be critical in selecting only the most advanced follicle to proceed to
ovulation. At the end of the luteal phase, there is a slight rise in FSH that seems to be of importance to start the next ovulatory cycle.

Control of FSH release from the pituitary gland is unknown. Low frequency gonadotropin-releasing hormone (GnRH) pulses increase FSH mRNA levels in the rat. GnRH has been shown to play an important role in the secretion of FSH, with hypothalamic-pituitary disconnection leading to a cessation of FSH. GnRH administration leads to a return of FSH secretion. FSH is subject to oestrogen feed-back from the gonads via the hypothalamic pituitary gonadal axis.

**Reference ranges for the blood content of follicle-stimulating hormone levels during the menstrual cycle.**

The ranges denoted By biological stage may be used in closely monitored menstrual cycles in regard to other markers of its biological progression, with the time scale being compressed or stretched to how much faster or slower, respectively, the cycle progresses compared to an average cycle. The ranges denoted Inter-cycle variability are more appropriate to use in non-monitored cycles with only the beginning of menstruation known, but where the woman accurately knows her average cycle lengths and time of ovulation, and that they are somewhat averagely regular, with the time scale being compressed or stretched to how much a woman's average cycle length is shorter or longer, respectively, than the average of the population. The ranges denoted Inter-woman variability are more appropriate to use when the average cycle lengths and time of ovulation are unknown, but only the beginning of menstruation is given.
Effects in females

FSH stimulates the growth and recruitment of immature ovarian follicles in the ovary. In early (small) antral follicles, FSH is the major survival factor that rescues the small antral follicles (2–5 mm in diameter for humans) from apoptosis (programmed death of the somatic cells of the follicle and oocyte). In the luteal-follicle phase transition period the serum levels of progesterone and estrogen (primarily estradiol) decrease and no longer suppress the release of FSH. The cohort of small antral follicles is normally sufficiently in number to produce enough Inhibin B to lower FSH serum levels. In addition, there is evidence that gonadotrophin surge-attenuating factor produced by small follicles during the first half of the follicle phase also exerts a negative feedback on pulsatile luteinizing hormone (LH) secretion amplitude, thus allowing a more favorable environment for follicle growth and preventing premature luteinization. As a woman nears perimenopause, the number of small antral follicles recruited in each cycle diminishes and consequently insufficient Inhibin B is produced to fully lower FSH and the serum level of FSH begins to rise. Eventually the FSH level becomes so high that downregulation of FSH receptors occurs and by menopause any remaining small secondary follicles no longer have FSH receptors. When the follicle matures and reaches 8–10 mm in diameter it starts to secrete significant amounts of estradiol. Normally in humans only one follicle becomes dominant and survives to grow to 18–30 mm in size and ovulate, the remaining follicles in the cohort
undergo atresia. The sharp increase in estradiol production by the dominant follicle cause a positive effect on the hypothalamus and pituitary and rapid GnRH pulses occur and an LH surge results. The increase in serum estradiol levels cause a decrease in FSH production by inhibiting GnRH production in the hypothalamus.

**Estradiol**

Estradiol or more precisely, 17β-estradiol, is a human sex hormone and steroid, and the primary female sex hormone. It is named for and is important in the regulation of the estrous and menstrual female reproductive cycles. Estradiol is essential for the development and maintenance of female reproductive tissues but it also has important effects in many other tissues including bone. While estrogen levels in men are lower compared to women, estrogens have essential functions in men as well. Estradiol is produced especially within the follicles of female ovaries, but also in other endocrine and non-endocrine tissues. Estradiol is biosynthesized from progesterone. One principle pathway then converts progesterone to its 17-hydroxy-derivative, and then to androstenedione via sequential cytochrome P450-catalyzed oxidations. Action of aromatase on this dione generates estrone, and action of a dehydrogenase on this gives the title compound, 17β-estradiol.

**Activity**

**Female reproduction**

In the female, estradiol acts as a growth hormone for tissue of the reproductive organs, supporting the lining of the vagina, the cervical glands, the endometrium, and the lining of the fallopian tubes. It enhances growth of the myometrium. Estradiol appears necessary to maintain oocytes in the ovary. During the menstrual cycle, estradiol produced by the
growing follicle triggers, via a positive feedback system, the hypothalamic-pituitary events that lead to the luteinizing hormone surge, inducing ovulation. In the luteal phase, estradiol, in conjunction with progesterone, prepares the endometrium for implantation. During pregnancy, estradiol increases due to placental production. In baboons, blocking of estrogen production leads to pregnancy loss, suggesting estradiol has a role in the maintenance of pregnancy. Research is investigating the role of estrogens in the process of initiation of labor. Actions of estradiol are required before the exposure of progesterone in the luteal phase.

**Sexual development**

The development of secondary sex characteristics in women is driven by estrogens, to be specific, estradiol. These changes are initiated at the time of puberty, most are enhanced during the reproductive years, and become less pronounced with declining estradiol support after the menopause. Thus, estradiol enhances breast development, and is responsible for changes in the body shape, affecting bones, joints and fat deposition. Fat structure and skin composition are modified by estradiol.

**Male reproduction**

The effect of estradiol (and estrogens) upon male reproduction is complex. Estradiol is produced by action of aromatase mainly in the Leydig cells of the mammalian testis, but also by some germ cells and the Sertoli cells of immature mammals. It functions to prevent apoptosis of male sperm cells.

Several studies have noted sperm counts have been declining in many parts of the world, and estrogen exposure in the environment has been postulated to be the cause. Suppression of estradiol production in a subpopulation of sub fertile men may improve the semen
analysis. Males with sex chromosome genetic conditions, such as Klinefelters syndrome, will have a higher level of estradiol.

**Testosterone**

Testosterone is a steroid hormone from the androgen group and is found in mammals. Testosterone is secreted primarily by the testicles of males and the ovaries of females, although small amounts are also secreted by the adrenal glands. It is the principal male sex hormone and an anabolic steroid. In men, testosterone plays a key role in the development of male reproductive tissues such as the testis and prostate as well as promoting secondary sexual characteristics such as increased muscle, bone mass, and the growth of body hair. In addition, testosterone is essential for health and well-being as well as the prevention of osteoporosis.

**Biological uses**

Testosterone is necessary for normal sperm development. It activates genes in Sertoli cells, which promote differentiation of spermatogonia.

- Regulates acute HPA (Hypothalamic–pituitary–adrenal axis) response under dominance challenge.

- Regulator of cognitive and physical energy

- Maintenance of muscle trophism

- Testosterone regulates the population of thromboxane A2 receptors on megakaryocytes and platelets and hence platelet aggregation in humans

**Regulation**
In males, testosterone is synthesized primarily in Leydig cells. The number of Leydig cells in turn is regulated by luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In addition, the amount of testosterone produced by existing Leydig cells is under the control of LH, which regulates the expression of 17-β hydroxysteroid dehydrogenase. The amount of testosterone synthesized is regulated by the hypothalamic–pituitary–testicular axis (see figure to the right). When testosterone levels are low, gonadotropin-releasing hormone (GnRH) is released by the hypothalamus, which in turn stimulates the pituitary gland to release FSH and LH. These latter two hormones stimulate the testis to synthesize testosterone. Finally, increasing levels of testosterone through a negative feedback loop act on the hypothalamus and pituitary to inhibit the release of GnRH and FSH/LH, respectively.

**Factors affecting testosterone levels include:**

- Weight loss may result in an increase in testosterone levels. Fat cells synthesize the enzyme aromatase, which converts testosterone, the male sex hormone, into estradiol, the female sex hormone.

- The secosteroid vitamin D in levels of 400–1000 IU/d (10–25 µg/d) raises testosterone levels.
Zinc deficiency lowers testosterone levels but over supplementation has no effect on serum testosterone.

Aging reduces testosterone release.

Hypogonadism

Sleep (REM dream) increases nocturnal testosterone levels.

**Mechanism of action**

The effects of testosterone in humans and other vertebrates occur by way of two main mechanisms: by activation of the androgen receptor (directly or as DHT), and by conversion to estradiol and activation of certain estrogen receptors.

Free testosterone (T) is transported into the cytoplasm of target tissue cells, where it can bind to the androgen receptor, or can be reduced to 5α-dihydrotestosterone (DHT) by the cytoplasmic enzyme 5-alpha reductase. DHT binds to the same androgen receptor even more strongly than testosterone, so that its androgenic potency is about 5 times that of T. The T-receptor or DHT-receptor complex undergoes a structural change that allows it to move into the cell nucleus and bind directly to specific nucleotide sequences of the chromosomal DNA. The areas of binding are called hormone response elements (HREs), and influence transcriptional activity of certain genes, producing the androgen effects.

Androgen receptors occur in many different vertebrate body system tissues, and both males and females respond similarly to similar levels. Greatly differing amounts of testosterone prenatally, at puberty, and throughout life account for a share of biological differences between males and females.
The bones and the brain are two important tissues in humans where the primary effect of testosterone is by way of aromatization to estradiol. In the bones, estradiol accelerates ossification of cartilage into bone, leading to closure of the epiphyses and conclusion of growth. In the central nervous system, testosterone is aromatized to estradiol. Estradiol rather than testosterone serves as the most important feedback signal to the hypothalamus.

**Early infancy**

Early infancy androgen effects are the least understood. In the first weeks of life for male infants, testosterone levels rise. The levels remain in a pubertal range for a few months, but usually reach the barely detectable levels of childhood by 4–6 months of age. The function of this rise in humans is unknown. It has been speculated that "brain masculinization" is occurring since no significant changes have been identified in other parts of the body. It is interesting to note that the male brain is masculinized by the aromatization of testosterone into estrogen, which crosses the blood–brain barrier and enters the male brain, whereas female fetuses have alpha-fetoprotein, which binds the estrogen so that female brains are not affected.

**Pre-peripubertal**

Pre-Peripubertal effects are the first observable effects of rising androgen levels at the end of childhood, occurring in both boys and girls.

**Adult-type body odor**

**Increased oiliness of skin and hair, acne**

**Pubarche (appearance of pubic hair)**
Axillary hair

Growth spurt, accelerated bone maturation

Hair on upper lip, on chin, and growth of sideburns.

Pubertal

Pubertal effects begin to occur when androgen has been higher than normal adult female levels for months or years. In males, these are usual late pubertal effects, and occur in women after prolonged periods of heightened levels of free testosterone in the blood.

Enlargement of sebaceous glands. This might cause acne.

Phallic enlargement or clitoromegaly

Increased libido and frequency of erection or clitoral engorgement

Pubic hair extends to thighs and up toward umbilicus

Facial hair (sideburns, beard, moustache)

Loss of scalp hair (Androgenetic alopecia)

Chest hair, periareolar hair, perianal hair

Leg hair

Axillary hair

Subcutaneous fat in face decreases

Increased muscle strength and mass\(^{[19]}\)
Deepening of voice

Growth of the Adam's apple

Growth of spermatogenic tissue in testicles, male fertility

Growth of jaw, brow, chin, nose, and remodeling of facial bone contours

Shoulders become broader and rib cage expands

Completion of bone maturation and termination of growth. This occurs indirectly via estradiol metabolites and hence more gradually in men than women.

**Adult**

Adult testosterone effects are more clearly demonstrable in males than in females, but are likely important to both sexes. Some of these effects may decline as testosterone levels decrease in the later decades of adult life.

**Prolactin**

Prolactin (PRL), also known as luteotropic hormone or luteotropin, is a protein that in humans is best known for its role in enabling female mammals to produce milk, however, it is influential over a large number of functions with over 300 separate actions of PRL having been reported in various vertebrates. Prolactin is secreted from the pituitary gland in response to eating, mating, estrogen treatment, ovulation, and nursing. Prolactin is secreted in a pulsatile fashion in between these events. Prolactin also plays an
essential role in: metabolism; regulation of the immune system; and pancreatic development.

Although often associated with human milk production, prolactin plays a wide range of other roles in both humans and other vertebrates. Prolactin also acts in a cytokine-like manner and as an important regulator of the immune system. It has important cell cycle related functions as a growth-, differentiating- and anti-apoptotic factor. As a growth factor, binding to cytokine like receptors, it also has profound influence on hematopoiesis, angiogenesis and is involved in the regulation of blood clotting through several pathways. The hormone acts in endocrine, autocrine, and paracrine manner through the prolactin receptor and a large number of cytokine receptors.

Pituitary prolactin secretion is regulated by endocrine neurons in the hypothalamus.

**Structure and isoforms**

The structure of prolactin is similar to that of growth hormone and placental lactogen. The molecule is folded due to the activity of three disulfide bonds. Significant heterogeneity of the molecule has been described, thus bioassays and immunoassays can give different results due to differing glycosylation, phosphorylation, sulfation, as well as degradation. The non-glycosylated form of prolactin is the dominant form of prolactin that is secreted by the pituitary gland. There are mainly three different forms of prolactin in regard to size:

Little prolactin is the predominant form. It has a molecular weight of approximately 22-kDa. It is a single-chain polypeptide of 198 amino acids, and is apparently the result of removal of some amino acids.
Pit-1 is a transcription factor that binds to the prolactin gene at several sites to allow for the production of prolactin in the pituitary gland. A key regulator of prolactin production is estrogens that enhance growth of prolactin-producing cells and stimulate prolactin production directly, as well as suppressing dopamine. Human prolactin receptors are insensitive to mouse prolactin.

Activity

Prolactin has a wide range of effects. It stimulates the mammary glands to produce milk (lactation): increased serum concentrations of prolactin during pregnancy cause enlargement of the mammary glands of the breasts and prepare for the production of milk. Milk production normally starts when the levels of progesterone fall by the end of pregnancy and a suckling stimulus is present. Sometimes, newborn babies (males as well as females) secrete a milky substance from their nipples known as witch's milk. This is in part caused by maternal prolactin and other hormones. Prolactin provides the body with sexual gratification after sexual acts: The hormone counteracts the effect of dopamine, which is responsible for sexual arousal. This is thought to cause the sexual refractory period. The amount of prolactin can be an indicator for the amount of sexual satisfaction and relaxation. Unusually high amounts are suspected to be responsible for impotence and loss of libido. Highly elevated levels of prolactin decrease the levels of sex hormones — estrogen in women and testosterone in men. The effects of mildly elevated levels of prolactin are much more variable, in women both substantial increase or decrease of estrogen levels may result.
Prolactin is sometimes classified as a gonadotropin although in humans it has only a weak luteotropic effect while the effect of suppressing classical gonadotropic hormones is more important. Prolactin within the normal reference ranges can act as a weak gonadotropin but at the same time suppresses GnRH secretion. The exact mechanism by which it inhibits GnRH is poorly understood although expression of prolactin receptors (PRL-R) have been demonstrated in rat's hypothalmus, the same has not been observed in GnRH neurons. Physiologic levels of prolactin in males enhance luteinizing hormone-receptors in Leydig cells, resulting in testosterone secretion, which leads to spermatogenesis.

Prolactin also stimulates proliferation of oligodendrocyte precursor cells. These cells differentiate into oligodendrocytes, the cells responsible for the formation of myelin coatings on axons in the central nervous system. Prolactin also has a number of other effects including contributing to surfactant synthesis of the fetal lungs at the end of the pregnancy and immune tolerance of the fetus by the maternal organism during pregnancy. Prolactin promotes neurogenesis in maternal and fetal brains.

**Production and regulation**

In humans, prolactin is produced at least in the pituitary, decidua, myometrium, breast, lymphocytes, leukocytes and prostate. Pituitary PRL is controlled by the Pit-1 transcription factor and ultimately dopamine, extrapituitary PRL is controlled by a superdistal promoter and apparently unaffected by dopamine.

In decidual cells and in lymphocytes the distal promoter and thus prolactin expression is stimulated by cAMP. Responsiveness to cAMP. Progesterone has been observed to upregulate prolactin synthesis in the endometrium but decreases it in myometrium and breast glandular tissue. Extra pituitary production of prolactin is thought to be special to humans and primates and may serve mostly tissue specific paracrine and autocrine
purposes. It has been hypothesized that in other vertebrates such as mice a similar tissue specific effect is achieved by a large family of prolactin like proteins controlled by at least 26 paralogous PRL genes not present in primates.