PART ONE

Normal Anatomy and Physiology Review

The focus of this section is the effect of female gender on human physiology, including the endocrine system, the reproductive tract, and the urinary tract. Other aspects of physiology, such as the cardiovascular system, are integrated into the text of the relative chapter.

CHAPTER 1

Endocrine System

Hypothalamus–Pituitary–Thyroid Axis
Hypothalamus–Pituitary–Adrenal Axis
Hypothalamus–Pituitary–Gonadal Axis
Gonadal Hormones
Adrenal Hormones
Dehydroepiandrosterone
Thyroid Hormones
Insulin

The endocrine and neuroendocrine systems include the hypothalamic–pituitary–adrenal axis, the hypothalamic–pituitary–thyroid axis, and the hypothalamic–pituitary–gonadal axis, complex systems of nerves and organs that secrete hormones into the bloodstream and influence multiple functions. The pineal gland and the gastrointestinal tract are also components of the endocrine system.

Hypothalamus–Pituitary–Thyroid Axis

The hypothalamic–pituitary–thyroid (HPT) axis is a self-regulating system that controls metabolism. In response to low levels of circulating thyroid hormone, the hypothalamus secretes thyrotropin-releasing hormone (TRH), which causes the anterior pituitary to secrete thyroid-stimulating hormone (TSH). TSH stimulates the thyroid gland to synthesize and secrete the thyroid hormones. As the levels of thyroid hormone increase, a negative-feedback mechanism impedes the further release of TRH and TSH.

Hypothalamus–Pituitary–Adrenal Axis

The hypothalamus–pituitary–adrenal (HPA) axis is a self-regulating system that is responsible for regulating stress responses, immune function, digestion, energy expenditure, and several adaptation responses. In response to low levels of corticosteroids or physical or emotional stress, the hypothalamus secretes corticotrophin-releasing factor (CRH). CRH causes the anterior pituitary to secrete several hormones, including adrenocorticotropic hormone (ACTH), which stimulates cortisol release from the adrenal glands.

Hypothalamus–Pituitary–Gonadal Axis

The hypothalamic–pituitary–gonadal (HPG) axis primarily regulates the reproductive system, but it also has a significant influence on the immune system. In response to low levels of estrogen and progesterone, the hypothalamus secretes gonadotropin-releasing hormone (GNRH). GNRH is released in pulses and initiates the release of follicle-stimulating hormone (FSH) and luteinizing

hormone (LH) from the anterior pituitary. FSH and LH initiate ovarian follicular development and ovulation and cause the synthesis and release of estrogens, progesterone, and testosterone. As the levels of these three hormones increase, a negative-feedback mechanism impedes the further release of FSH and LH.

Gonadal Hormones

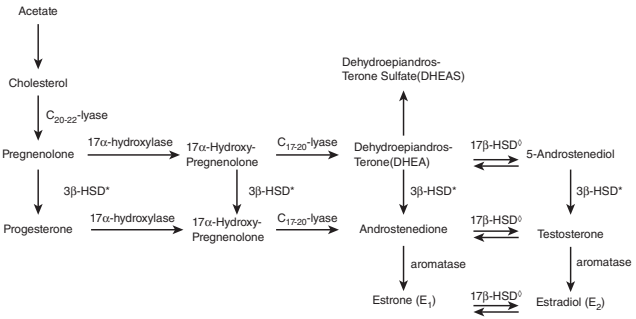
Estrogen

Estrogen is a steroid hormone produced primarily in the ovaries, breasts, and adipose tissue and in smaller quantities in the skin, liver, brain, and intestines. Estrogen has significant effects in the female reproductive system. The three major estrogen derivatives are estrone (E1), estradiol (E2), and estriol (E3). Estrone is the primary form of estrogen after menopause, estradiol is the primary form of estrogen prior to menopause, and estriol is a byproduct of estrogen metabolism that is also produced by the placenta during pregnancy.

Estrogen is synthesized from low-density lipoprotein (LDL) cholesterol in reactions that require transportation of cholesterol across the cellular membrane via a delivery mechanism that is influenced by LH, ACTH, cyclic adenosine monophosphate (AMP), and calcium. Cholesterol is converted to pregnenolone and subsequently to progesterone, androgens, estrogens, and corticosteroids. See Figure 1-1.

Estradiol—Fast Facts

- The most potent of the estrogens occurring naturally in the body
- Primary hormone produced by the ovaries during the reproductive years
- Primary hormone responsible for the menstrual cycle
- Impacts bone, blood vessels, heart, brain, and skin health
- In function intensity, 12 times stronger than estrone and 80 times stronger than estriol
- Responsible for growth and female development
- Increases the amount of fat in subcutaneous tissues, especially the breasts, thighs, and buttocks



*3β-HSD=3β-hydroxysteroid dehydrogenase-$\Delta^{5,4}$-isomerase
◊17β-hydroxysteroid dehydrogenase

Figure 1-1 Steroidogenic pathways.

Reproduced from Homburg, R. (2008). The mechanism of ovulation. In Glob. libr. women's med., (ISSN: 1756-2228). Retrieved from http://editorial.glowm.com/?p=glowm.cml/section_view&articleid=289; Roy Homburg, "Ovulation Induction and Controlled Ovarian Stimulation – A Practical Guide" published by Taylor & Francis (now Informa), 2005. ISBN 1-84184-429-2

- Influences hip-bone formation, resulting in the characteristic female skeletal development
- Can be converted to estrone in the liver, breast, and other peripheral tissues

Estrone—Fast Facts

- Primarily an adrenal-derived estrogen
- Can be converted to estradiol
- Dominates in menopausal women

Estriol—Fast Facts

- A weak estrogen
- Produced in large amounts by the placenta and can be detected by the ninth week of pregnancy
- May be measured in urine
- The most abundant estrogen

Progesterone

Progesterone is a steroid hormone that facilitates female reproductive physiology. It is synthesized in the ovaries and secreted by the corpus luteum following ovulation. Like estrogen, progesterone affects multiple tissues and organs, including the brain, breast, uterus, ovary, and cervix.

Progesterone—Fast Facts

- In the uterus and ovary, progesterone initiates the release of mature oocytes, facilitates implantation of the zygote, and maintains pregnancy by promoting uterine growth and suppressing muscle contractility.
- In the breast, progesterone facilitates glandular development in preparation for milk secretion and the suppression of milk protein synthesis before childbirth.
- In the brain, progesterone mediates signals required for sexually responsive behavior.
- In bone tissue, progesterone modulates bone mass.

The release of progesterone by the corpus luteum is facilitated by LH. The function of LH is mediated by cAMP, FSH, adrenal hormones, prolactin, prostaglandins, and activin. Progesterone is transported through the blood bound to corticosteroid-binding globulin (transcortin). Progesterone's actions and effects are subjected to its nuclear receptor. Progesterone receptors are proteins that are influenced by estrogen to bind progesterone. Progesterone receptors are widely distributed throughout the body and regulate the functions of thyroid hormones, vitamin D, steroids, and retinoids, among others.

Testosterone

Testosterone is an androgen produced primarily by the ovaries but also by the adrenal glands through peripheral conversion of androstenedione to testosterone in adipose tissue. Under the influence of LH, the ovaries secrete 25% of circulating testosterone and 50% of the body's androstenedione. The adrenals secrete another 25% of the body's testosterone.

In healthy women, the majority of testosterone is bound to sex hormone-binding globulin (SHBG), with significantly smaller amounts bound to albumin or circulating freely in the bloodstream.

Androgen receptors have been identified in multiple tissues, including the skin, the brain, the cardiovascular system, adipose tissue, skeletal muscle, and the gut. Testosterone and dihydrotestosterone (DHT) are the only androgens currently known to activate androgen receptors. DHT is more potent than testosterone.

Testosterone—Fast Facts

- Produced peripherally in the skin, liver, adipose tissue, and urogenital system
- Androstenedione and, to some degree, dehydroepiandrosterone (DHEA) are converted to testosterone in the skin.

CLINICAL PEARL

There is no feedback regulatory loop controlling androgen secretion in women. The extent to which a female expresses androgenicity is dependent on the amount of free circulating testosterone.

Adrenal Hormones

The adrenal steroid hormones are the glucocorticoids, cortisol (hydrocortisone), and the mineralocorticoids (aldosterone). They are synthesized from cholesterol and transported through the blood bound to corticosteroid-binding globulin, a carrier protein that is synthesized by the liver. Their actions are dependent on the type of receptor to which they bind.

Glucocorticoids—Fast Facts

- Cause the liver to convert muscle protein and fat to glucose
- Influence the conversion of sugars, fats, and proteins to energy

- Suppress immune responses
- Inhibit swelling and inflammation
- Provide energy needed in response to emotional and physical stress; balance the stress response
- Speed up metabolism
- Influence liver metabolism of stored glucose
- Control temperature (catecholamine-mediated mobilization of free fatty acids for the shivering response; enhanced blood and liver carbohydrate levels during hypothermia)

CLINICAL PEARL

Cortisol is the most abundant and potent of the glucocorticoids. Too much cortisol is a cause of Cushing's syndrome, and too little cortisol is a cause of Addison's disease.

Mineralocorticoids—Fast Facts

- Facilitate sodium retention
- Facilitate potassium and hydrogen excretion
- Maintain water balance

CLINICAL PEARL

Persistently elevated levels of glucocorticoids impede other steroid hormones and can cause infertility.

Excess mineralocorticoid activity may result in systemic edema and elevated blood pressure.

Dehydroepiandrosterone

DHEA is produced primarily by the adrenal glands, with smaller amounts produced by peripheral conversion from ovarian secretions. The ovaries secrete 20% of the body's DHEA. DHEA,

dehydroepiandrosterone sulfate (DHEAS), and androstenedione are almost entirely bound to albumin and as such are readily available.

DHEA—Fast Facts

- Converted to androstenedione and subsequently to estrogen and testosterone
- May activate alpha and beta estrogen receptors
- Synthesis may be impacted by chronic stress, causing adrenal depletion as a result of cortisol production

Thyroid Hormones

Thyroid hormones are produced by the thyroid gland under the influence of TSH. They support almost all body systems. Thyroid hormones are made of iodine, which is ingested during daily food and water intake, and thyroglobulin, a substrate made of the amino acid tyrosine. Thyroxin (T4), the most abundant thyroid hormone, is composed of four iodine atoms. Triiodothyronine (T3), the most active form of thyroid hormone, is composed of three iodine atoms. Together, the thyroid hormones regulate growth, control metabolism, and control circadian rhythms.

After thyroid hormones are released into the bloodstream, thyroid transport proteins transport the hormones to a range of target cells. Conversion of T4 to T3 takes place in the target cells. T4 is also converted to various other thyroid hormones. The largest concentrations of thyroid hormone are found in the liver, muscles, and kidneys.

Thyroid Hormones—Fast Facts

- Bind to receptor cells and are activated in peripheral tissue
- May take hours to days to achieve their final effect on cell energy and metabolism
- Necessary for many functions, including the following:
  - Brain development
  - Axial skeleton development

- Metabolism of sugars, fats, and proteins
- Respiratory function
- Immune system function

Insulin

Insulin is a pancreatic hormone that is essential for the regulation of blood glucose. Lack of insulin and the inability to adequately respond to insulin are primary causes of diabetes.

Insulin has a similar function in males and females. However, insulin's ability to regulate blood sugar is significantly more challenging in females than in males because of the influence of female hormones on blood sugar.

Insulin—Fast Facts

- Regulates the body's use of glucose
- Controls blood sugar levels
- Regulates fat storage
- Provides the signals required by the liver, muscles, and fat to take in glucose from the blood
- Signals the liver to take in glucose and store it as glycogen