

Gonadotropins and steroidogenesis

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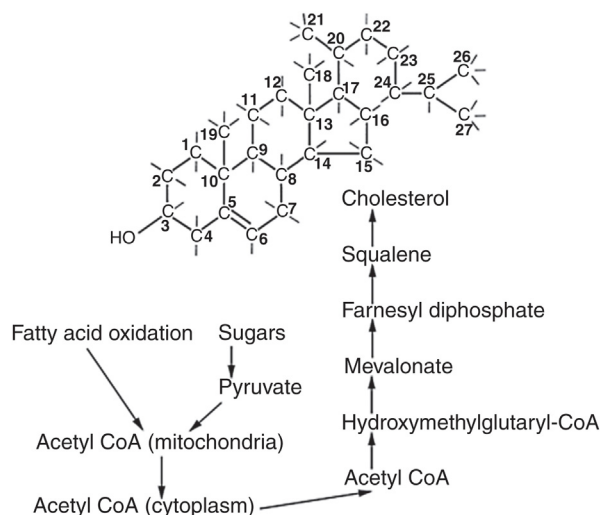
Estrogens and progestogens

The sex steroids are androgen, estrogens, and progestogens. They are all made from the root steroid cholesterol (Fig. 14.1). Cholesterol is always thought about in a negative sense, such as in vascular blockage, cranial vascular accident, and myocardial infarction. On the positive side, cholesterol is the root or mother steroid; there would be no sex steroids without cholesterol. As shown in Fig. 14.1, cholesterol is made from cytoplasmic Acetyl CoA. The constituents come from the oxidation of sugars or oxidative degradation of fatty acids as mitochondrial acetyl CoA that is transferred to the cytoplasm. Cholesterol carbons are numbered to a convention used in the naming and numbering of all steroids.

There are multiple types of progestogens. All these can be identified as 21 carbon steroids. Progestogens include progesterone and 17α -progesterone, the two biologically active natural progestogens (Fig. 14.2). Synthetic progestogen agonists used by steroid manufacturers include norethisterone and norethisterone, among others (Fig. 14.2). Similarly, there is not just one androgen. Natural androgens include testosterone, androstenedione, dehydroepiandrosterone (DHEA), DHEA-sulfate, and dihydrotestosterone. Androstanoalone is an example of a commercial androgen agonist. All androgens are characteristically 19 carbon steroids. There are three natural forms of estrogen; these are estrone or E1, estradiol or E2, and estriol or E3 (Fig. 14.2). To help remember their names, structures, and numbers, consider the following Fig. 14.3, estrONE or E1 contains one hydroxyl group, estradiOL or E2 contains two hydroxyl groups, and esTRIol or E3 contains three hydroxyl groups. Estrogens have two characteristics; are always 18 carbon steroids and always have an aromatized ring A.

All three estrogens are aromatized or made by the same aromatase enzyme (Fig. 14.3), but are made from different androgen substrates. Estrone (E1) is made by aromatase action on androstenedione, estradiol (E2) by aromatase action on testosterone, and estriol (E3) by aromatase action on 16α -dehydroxyandrostenedione. Ethinylestradiol is an example of a commercial estrogen agonist.

While detailed structures of the steroids and their synthesis pathways are not presented here, however, the basic features of sex steroids, progestogens 21 carbon structures, androgens 19 carbon structures, and estrogens 18 carbon structures with an aromatized ring are discussed.

**FIGURE 14.1**

The structure, synthesis, and carbon numbering of cholesterol.

PROGESTAGENS

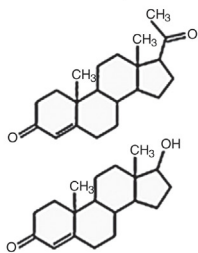
21 carbon steroids

Progesterone

17 α -progesterone

Norpregnene (commercial)

Norethisterone (commercial)

**ANDROGENS**

19 carbon steroids

Testosterone

Dehydroepiandrosterone (DHEA)

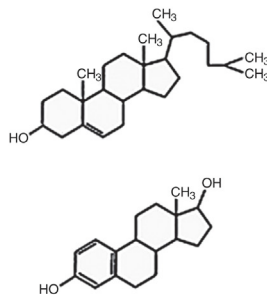
Dihydrotestosterone

Androstenedione

Androstanolone (commercial)

CHOLESTEROL

27 carbon steroids

**ESTROGENS**

18 carbon steroid

Estrone (E1)

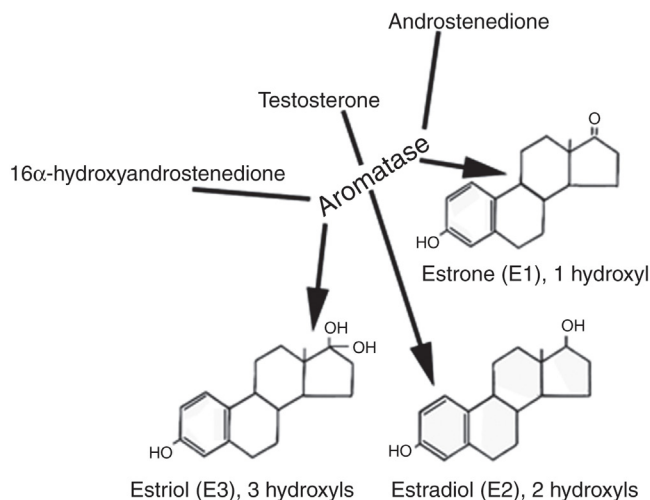
Estradiol (E2)

Estriol (E3)

Ethinyl estradiol (commercial)

FIGURE 14.2

Classes of sex steroid as identified by number of carbon atoms.

**FIGURE 14.3**

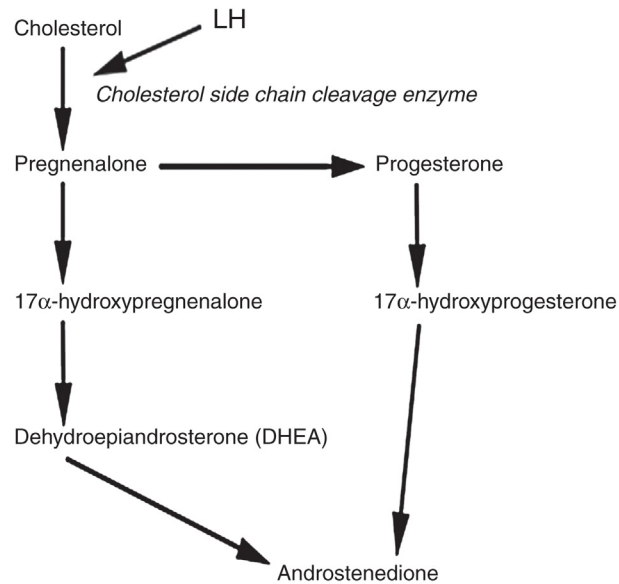
Aromatase can make estrone (E1), estradiol (E2), and estriol (E3).

Sex steroid synthesis by the ovary

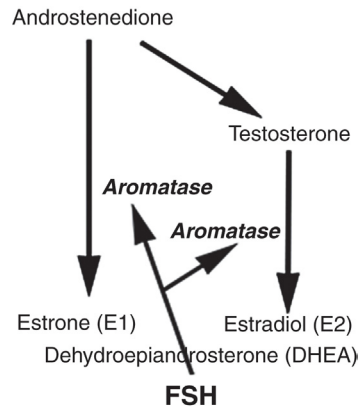
All female steroids important for the normal reproduction are produced in the ovary. In the follicular phase of the menstrual cycle, granulosa and theca cells work side by side in producing estrogens such as estradiol (E2). As shown in Fig. 14.4, two pathways generate the androgen androstenedione in theca cells. One pathway involves pregnenolone and progesterone and generation of the second form of progestogen 17 α -hydroxyprogesterone. The second path bypasses progesterone synthesis, involving 17 α -hydroxypregnenalone and the androgen dehydroepiandrosterone (DHEA) (Fig. 14.4). Both pathways make androstenedione and androgen. The key or rate-limiting step in all pathways is the generation of pregnenolone from cholesterol by cholesterol side-chain cleavage enzyme. All other enzymes are present, not controlled and fully active. Cholesterol side-chain cleavage enzyme is activated by luteinizing hormone (LH) or hCG binding to a LH/hCG receptor on theca cells.

Theca cells are enfolded around granulosa cells in ovarian follicles. Granulosa cells take up the androgen androstenedione made in theca cells, first convert it to testosterone and then aromatize it to the principal estrogen Estradiol (E2) (Fig. 14.5). Alternatively, androstenedione can be directly aromatized to estrone (E1). The limiting step in these pathways is aromatase, which is promoted by the FSH, binding its receptor on granulosa cells. Other steps are not regulated. Estradiol and estrone are the principal estrogens made during the menstrual cycle.

In the luteal phase of the menstrual cycle, progestogens are produced. Corpus luteal cells lack the enzyme activities needed to make androgens like androstenedione and just make progesterone and 17 α -hydroxyprogesterone (Fig. 14.6). Once

**FIGURE 14.4**

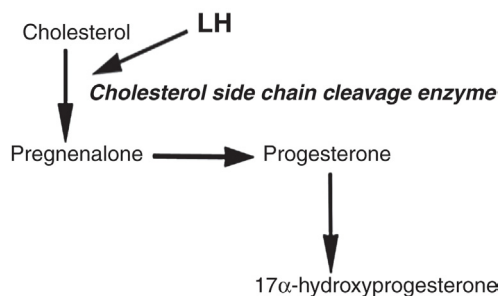
Sex steroid production in theca cells during the follicular phase of the menstrual cycle.

**FIGURE 14.5**

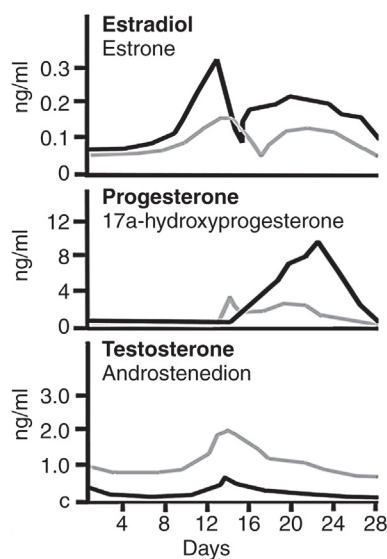
Sex steroid production in granulosa cells during the follicular phase of the menstrual cycle.

again the limiting factor is cholesterol side-chain cleavage enzyme, which is promoted by LH (Fig. 14.6).

With the assistance of LH and FSH, the ovary makes primarily estrone (E1) and estradiol (E2) and progesterone and 17 α -hydroxyprogesterone during the menstrual cycle. Other intermediates have biological functions. A small amount of testosterone

**FIGURE 14.6**

Sex steroid production by corpus luteal cells during the luteal phase of the menstrual cycle.

**FIGURE 14.7**

Mean sex steroid serum concentrations the mean menstrual cycle.

enters the blood and is used by the female reproductive biology, such as for muscular anabolism and for promoting female libido.

Fig. 14.7 shows mean sex steroid concentrations in the menstrual cycle. As shown, estradiol (E2) is the principal estrogen detected in serum. Estradiol levels in the follicular phase rise to a peak at around day 11. Estrone (E1) concentrations peak at around the time of ovulation at day 14. Both estradiol (E2) and estrone (E1) levels remain elevated in the luteal phase, rising to a peak around day 20–day 24 and then dropping down. On the progestogen side, progesterone predominates. Progesterone levels are virtually zero during the follicular phase. Starting with the LH,

peak levels rise continuously and peak around day 23. Levels then drop down after the peak. Levels of 17α -progesterone are very small, peaking with the LH peak and remaining elevated during the luteal phase. In the blood of females, androgen androstenedione is most evident. It is a weak androgen with 10% the biological potency of testosterone. Androstenedione concentrations in serum are mostly elevated at around 1 ng/mL during the follicular phase and luteal phase, with a peak around the time of ovulation. A tiny concentration of testosterone is present in serum, about 0.2 ng/mL in the follicular and luteal phase and peaking around the time of ovulation.

Sex steroid synthesis in pregnancy

In pregnancy, totally different pathways are activated for sex steroid synthesis (Fig. 14.8). The steroid synthesis pathway involves the mother, the placenta, and different fetal organs (Fig. 14.8). Progesterone production is maintained by the placenta from 7 weeks of pregnancy, or after corpus luteal progesterone production has finished, until term. The mother provides the placenta with cholesterol, and the placenta makes progesterone using the same pathway as used during the menstrual cycle by the corpus luteum (Fig. 14.8). The cholesterol side-chain cleavage enzyme is strongly promoted by the high levels of hCG made by the placenta during this time.

In the synthesis of estrone (E1) and estradiol (E2), the fetal adrenal gland and the maternal adrenal gland make a dehydroepiandrosterone-sulfate (DHEA-sulfate). This is the substrate. The placenta converts this molecule to androstenedione and testosterone. Then aromatase converts androstenedione and testosterone to estrone (E1) and estradiol (E2) (Fig. 14.8). High concentrations of estrogens are produced during pregnancy. The principal form of estrogen made in pregnancy is estriol (E3). Estriol (E3) is an estrogen with slight use in the menstrual cycle. The fetal adrenal makes DHEA-sulfate. This becomes hydroxylated in the fetal liver as 16α -hydroxydehydroepiandrosterone-sulfate. The fetal liver then produces 16α -hydroxyandrostenedione. This passes into the placenta where it is aromatized to estriol (E3) (Fig. 14.8).

Levels of progesterone and estriol produced in pregnancy rise continuously during the span of pregnancy. Progesterone levels in serum are approximately 20 ng/mL at 4 weeks gestation (weeks since last menstrual bleeding) and 180 ng/mL at 40 weeks of gestation. Estriol levels range from approximately 50 ng/mL at 28 weeks to 200 ng/mL at 40 weeks of pregnancy. Estriol assessment is used as a measure of fetal well being since the production of estriol requires appropriate fetal adrenal and fetal liver function.

Functions of sex steroids

The sex steroids have multiple functions in females. Sex steroids are lipids and can pass through the lipid bilayer on plasma membranes of cells. All sex steroids act on bivalent receptors within cells (Fig. 14.9). Upon binding to the receptor, the

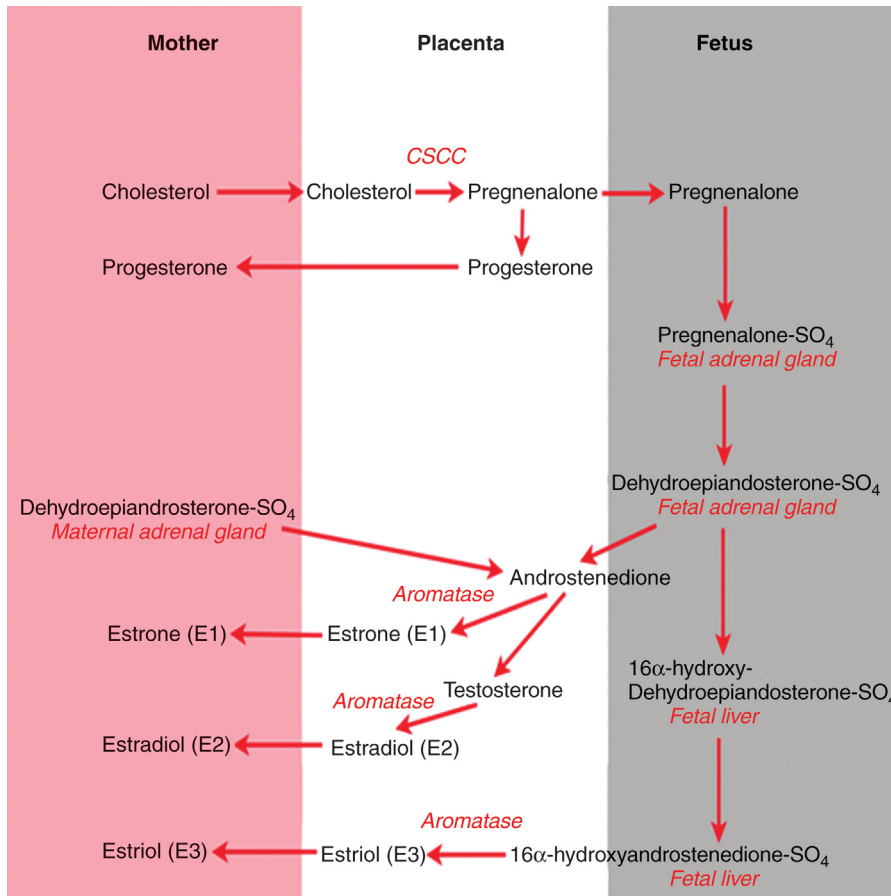


FIGURE 14.8

Sex steroid synthesis during pregnancy. Shows the combined maternal-placenta-fetus element needed to make sex steroids, particularly estriol (E3), the principal estrogen made in pregnancy. Cholesterol side-chain cleavage enzyme is *CSCC*.

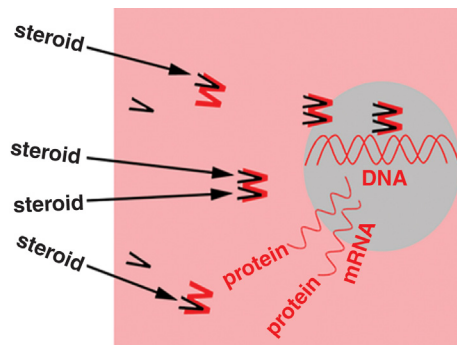


FIGURE 14.9

Sex steroid interaction with cytoplasmic bivalent receptors.

hormone–receptor complex is moved to the nucleus and promotes DNA transcription leading to the protein production (Fig. 14.9).

Sex steroid functions in the menstrual cycle and pregnancy

Estrogens modulate secondary sexual characteristics. These comprise enlargement of breasts and erection of nipples; growth of body hair, most prominently in underarms and pubic hair; greater development of thigh muscles and widening of hips; distribution of weight and body fat deposits around buttocks, thighs, and hips. In the follicular phase of the menstrual cycle, estrogens start growth of the glandular endometrial lining (Fig. 14.10). It is a function taken over by progesterone in the luteal phase of the menstrual cycle. At the end of the menstrual cycle, all gained lining is lost at menses.

Estrogens feed back to the hypothalamus in different ways. Low levels of estrogens like those observed in the follicular phase feed back to the hypothalamus and inhibit gonadotropin releasing hormone (GnRH) production. This reduces GnRH stimulation of gonadotropins. In contrast, high levels of estradiol as seen at the estradiol peak strongly promote GnRH pulses and pulse amplitude leading to the LH peak.

Estrogens also have a function in thrust of the ovum through the fallopian tube. Ampullary muscles of the fallopian tube are contracted in unison in response to estrogens leading to the ovum movement. Estradiol, the most potent natural estrogen

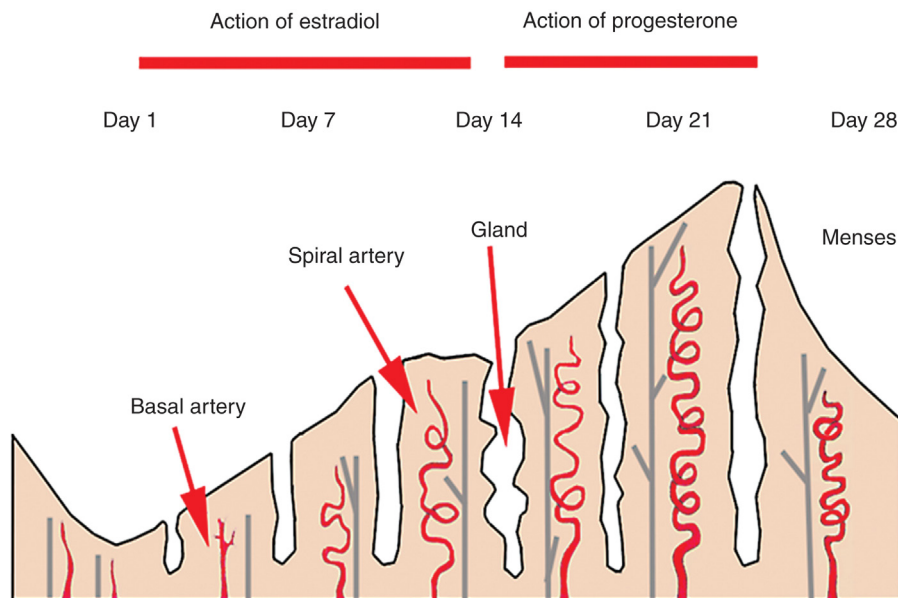


FIGURE 14.10

Endometrial lining of the uterus.

is mildly anabolic and promotes calcium uptake by bones. It is the absence of this calcium uptake during menopause which causes osteoporosis when estrogen levels decline. During pregnancy estrogens promote growth, mammary growth, and fetal nutrition.

Progestogens are primarily made in the luteal phase, where they promote the growth of the glandular endometrial lining of the uterus, supported by spiral arteries of the uterus (Fig. 14.10). This prepares the uterus for a possible implanting pregnancy. Progestogens, such as estrogens, feedback to the hypothalamus to modulate GnRH pulses. Progestogens, however, only suppress GnRH pulses.

Androgens also have functions in females; testosterone is an unconjugated steroid and is able to cross the blood–brain barrier, where it affects libido, sexual aggressiveness, and behavior. Androgens can also be anabolic in females, affecting calcium uptake by bone, hair, and muscle growth.

Male steroidogenesis

We consider the essential cells of the testis, Fig. 14.11. The Leydig cells are the site of action of LH or human chorionic gonadotropin (hCG) and the Sertoli cells are the sites of action of follicle-stimulating hormone (FSH). LHs (or hCGs) are the pituitary

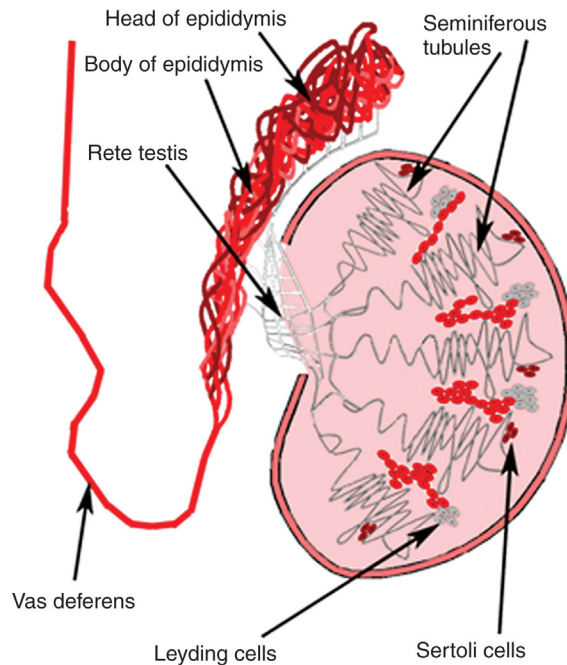
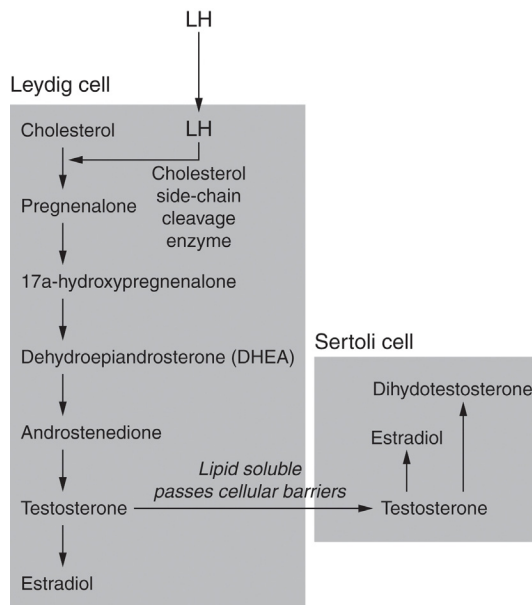


FIGURE 14.11

The testis dihydrotestosterone and estradiol.

**FIGURE 14.12**

Steroidogenesis in the postpubertal male.

hormones that promote steroidogenesis in males, while testosterone is made in Leydig cells, dihydrotestosterone is made in Sertoli cells (Fig. 14.11).

GnRH is released in pulses by the hypothalamus including LH (hCG) and FSH. LH (or hCG) directly promotes cholesterol side-chain cleavage enzyme in Leydig cells, changing cholesterol to pregnenolone (Fig. 14.12). The pregnenolone is converted to androstenedione like in theca cells in females, and then to testosterone (Fig. 14.12). The testosterone can be aromatized directly in the Leydig cells to make estradiol. Testosterone enters the blood from this point and gets transferred to the testis seminiferous tubules. Some testosterone gets transferred to Sertoli cells (Fig. 14.12), where it undergoes reduction to make the more active androgen, dihydrotestosterone and is aromatized to estradiol. Testosterone feeds back to the hypothalamus modulating GnRH pulses. The major difference between steroidogenesis in the male and female gonads is that testosterone production is continuous in the postpubertal male and not menstrual-cyclic as steroid in the postpubertal female.

Functions of androgens in males

As shown in Table 14.1, testosterone is the principal steroid produced by the testes on a constant, non-cyclic basis. Testosterone, complemented by dihydrotestosterone has the following functions in the adult male:

Table 14.1 Examines total levels of androgens and estrogens in male blood.

Steroid	Serum concentration (ng/mL)
Testosterone	2.6–10
Dihydrotestosterone	0.25–0.75
Androstenedione	0.5–2.5
Estradiol	0.01–0.05

1. Promotion of sperm development in seminiferous tubules.
2. Substrate for synthesis of more potent androgen dihydrotestosterone, and for aromatization to estrilol.
3. Secondary sexual characteristic in males, increase bone and muscular masses, and hair growth.
4. Libido development and promotion of penile erection.
5. Promotes adult male mental and physical energy. Questionable research suggests that it may have a role in the maintenance of cardiovascular health, and in risk taking.

Prenatally, testosterone is significant in genital virilization, development of the prostate and seminal vesicles and in gender identity. In the male fetus, testosterone promotes the differentiation of the Wolffian duct to form an epididymis and vas deferens.

During puberty testosterone causes enlargement of the sebaceous glands, promotes male libido, penile enlargement, increases facial hair, chest hair, leg hair, axillary hair, and jaw growth.

Functions of estrogens males

The function of estradiol formed normally in males is far from sure. Evidence suggests that estradiol has a role in the following:

1. Growth of penis
2. Development of testicles
3. Growth of hair
4. Deepening voice in men
5. Maturation of sperm.

More research is needed to confirm the exact function of estradiol in men.

Further reading

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