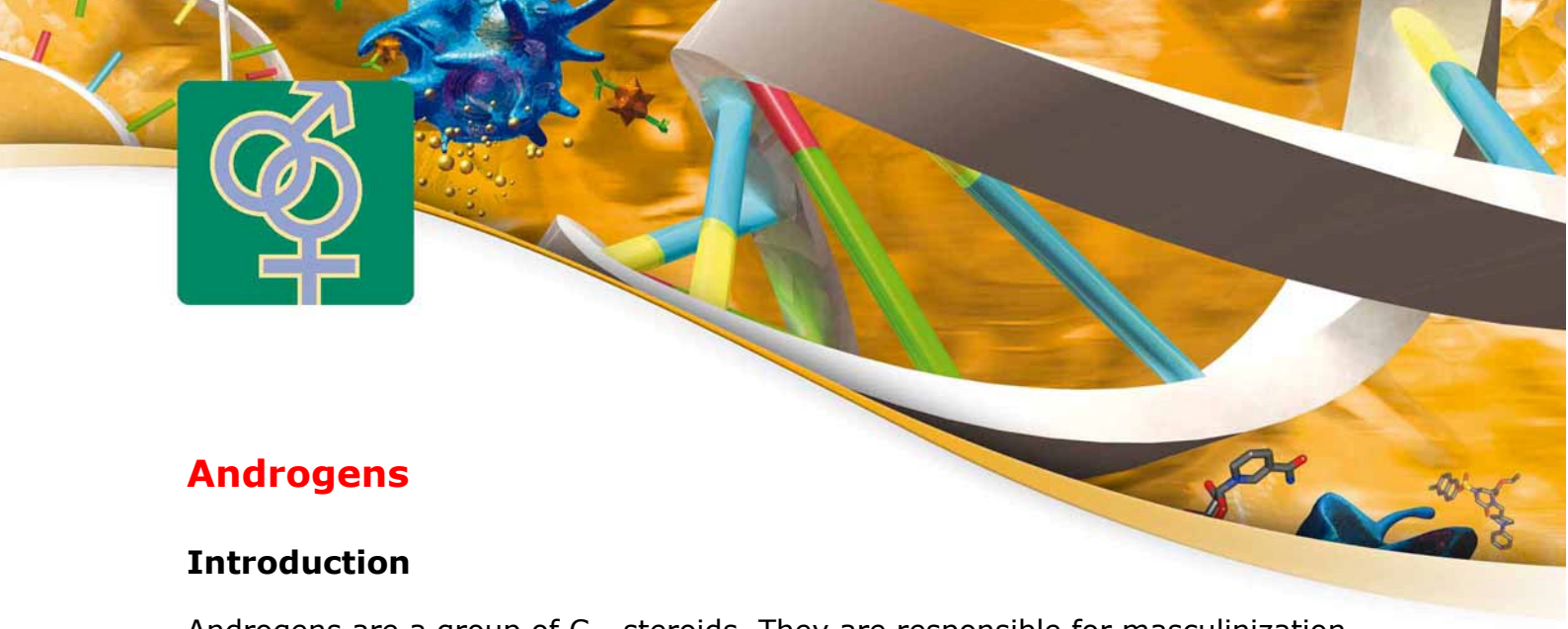
Reproductive

Androgens

Analytes Information

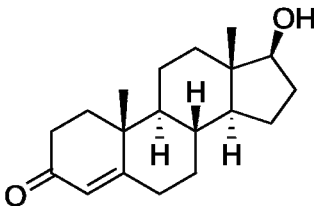


Androgens

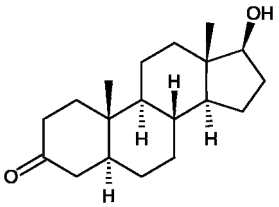
Introduction

Androgens are a group of C_{19} steroids. They are responsible for masculinization of the genital tract as well as the development and maintenance of male secondary sex characteristics. They contribute to muscle bulk, bone mass, libido and sexual performance in men.
Androgens also act as precursors to estrogens, the female sex hormones. The primary and best-known androgen is testosterone.
Testosterone and dihydrotestosterone are the most potent androgens in humans. Other important androgens are dehydroepindrosterone (DHEA), and androstenedione (ASD). (Fig. 1.)
Androgens are also known as androgenic hormones or testoids.

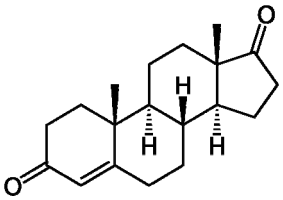
Fig.1: The formulas of the most common androgens



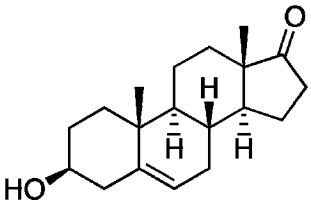
Testosterone



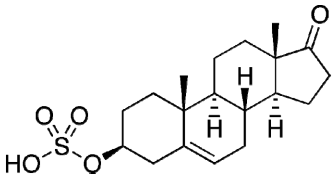
Dihydrotestosterone (DHT)



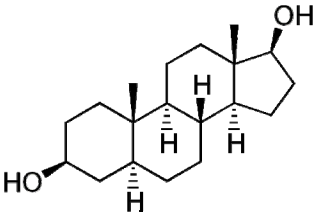
Androstenedione (ASD)



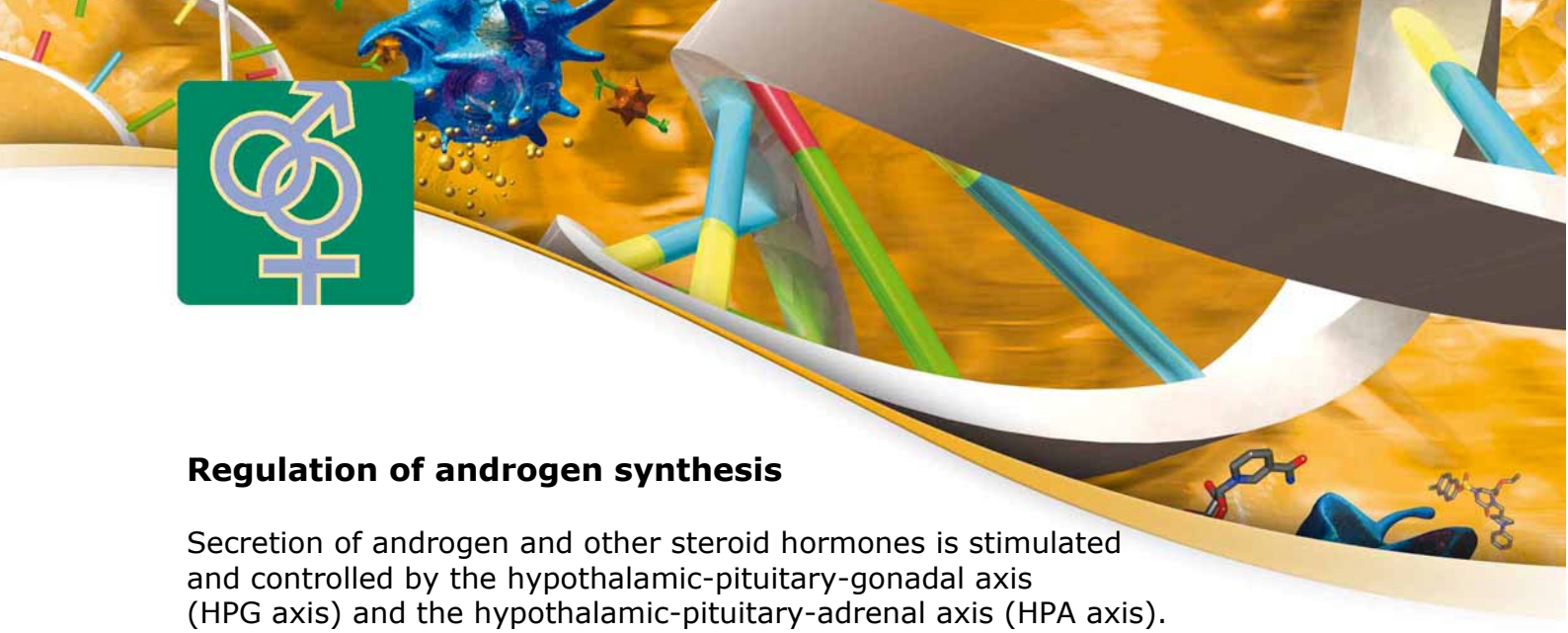
Dehydroepiandrosterone (DHEA)



Dehydroepiandrosterone sulfate (DHEA-S)



Androstanediol

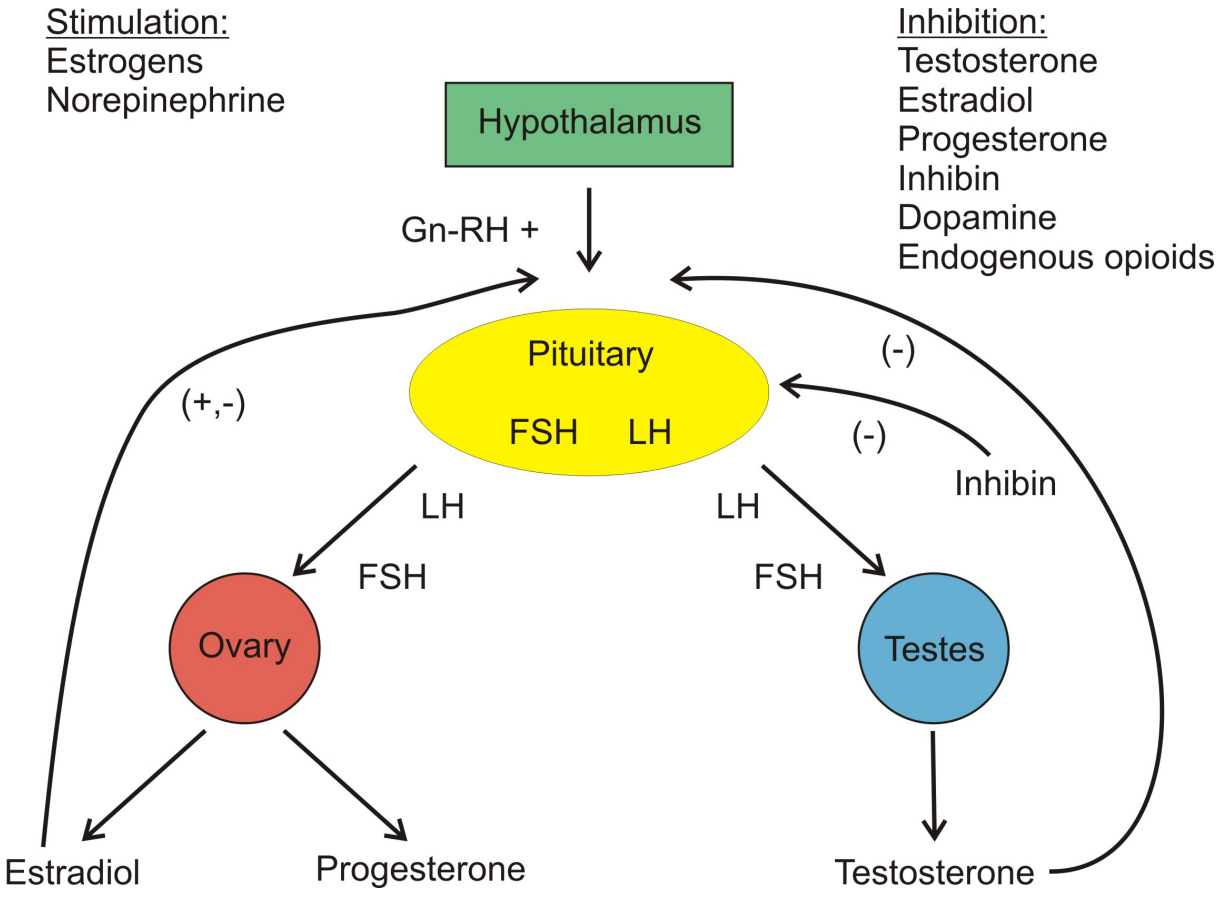


Regulation of androgen synthesis

Secretion of androgen and other steroid hormones is stimulated and controlled by the hypothalamic-pituitary-gonadal axis (HPG axis) and the hypothalamic-pituitary-adrenal axis (HPA axis).

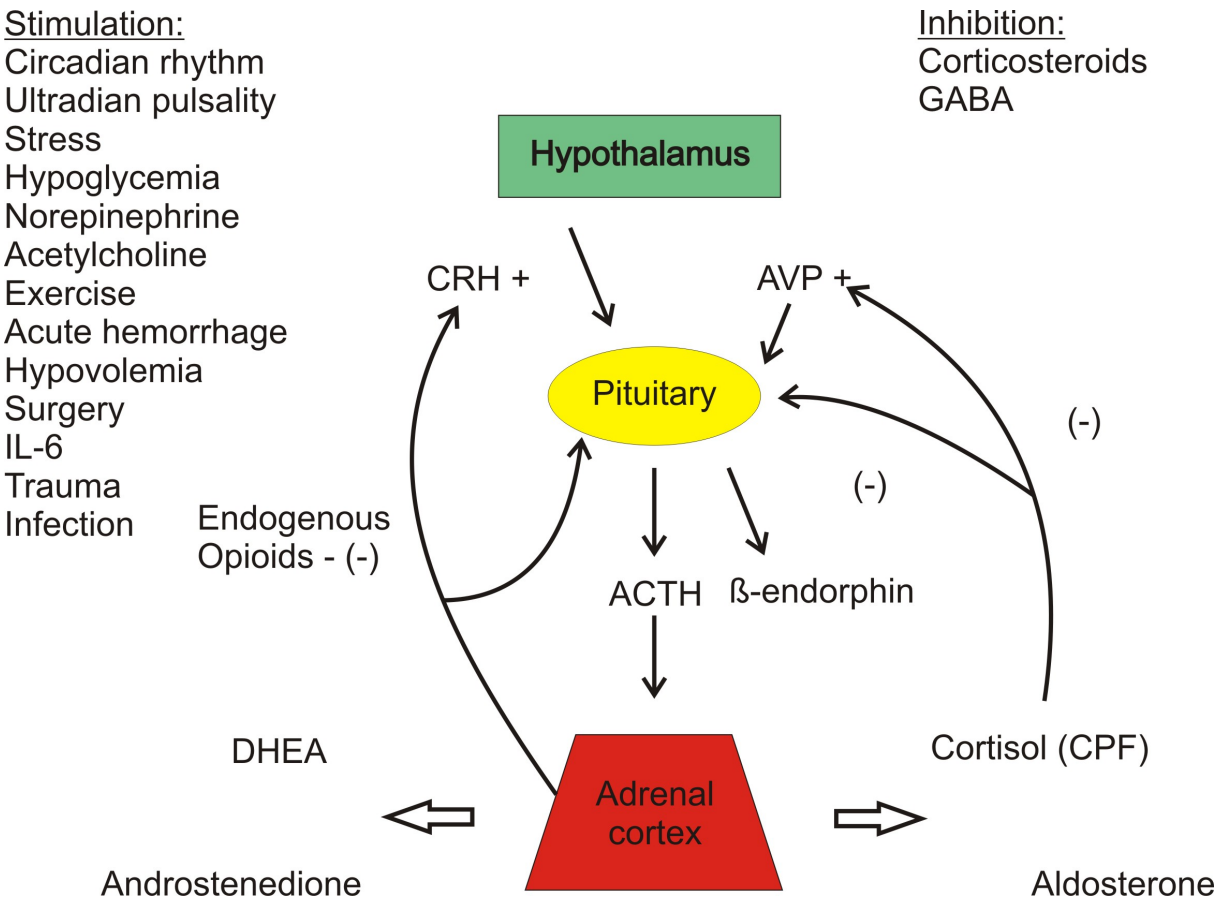
Hypothalamic-pituitary-gonadal axis (Fig.2)
This axis comprises the mutual interactions of the hypothalamus, pituitary gland and gonads. To a large extent, control of sexual function in both males and females begins with the secretion of gonadotropin-releasing hormone (GnRH) by the hypothalamus, which is invoked by neural and sensory inputs from the brain. GnRH stimulates the anterior pituitary gland to secrete the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH is the primary stimulus for androgen and estrogen secretion in testes and ovary, which in turn provides negative feedback on GnRH production.

Fig.2: The regulatory feedback loop of the HPG axis



Hypothalamic-pituitary-adrenal axis (Fig.3)
This axis comprises the mutual interactions of the hypothalamus, pituitary gland and adrenal glands. The HPA axis is a major part of the neuroendrocrine system that controls reactions to stress and regulates many body processes, including sexuality. Neural and others factors control pulsative and circadian secretion of corticotropin-releasing hormone (CRH). CRH and (to a lesser extent) arginine vasopressin (AVP), both produced in hypothalamus, stimulate the release of ACTH from the anterior pituitary gland. In turn, ACTH stimulates the adrenal cortex to secrete DHEA, DHEA-S, androstenedione, in addition to cortisol and aldosterone. Negative feedback on CRH, AVP, and ACTH production is provided by cortisol.

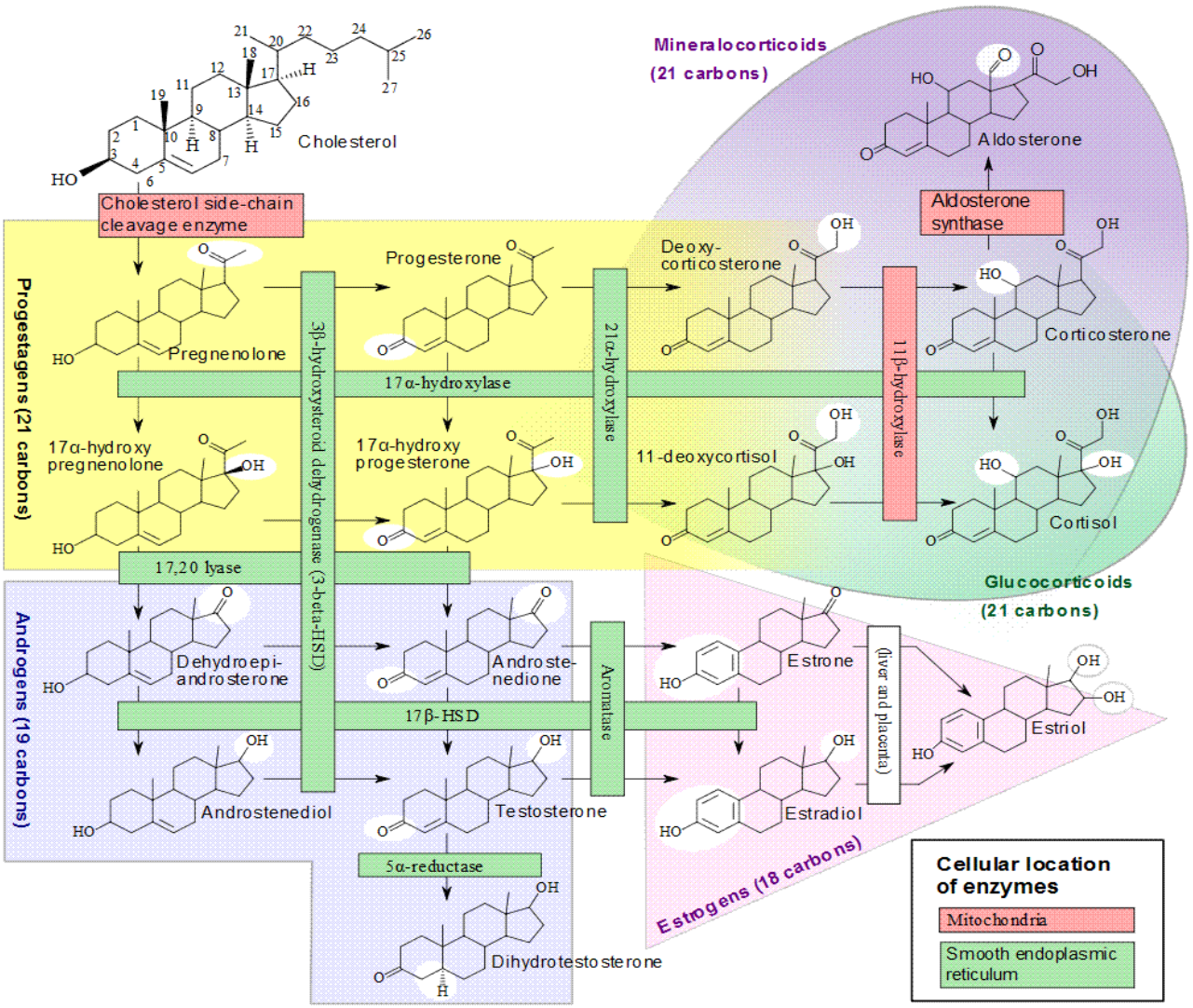
Fig.3: The regulatory feedback loop of the HPA axis

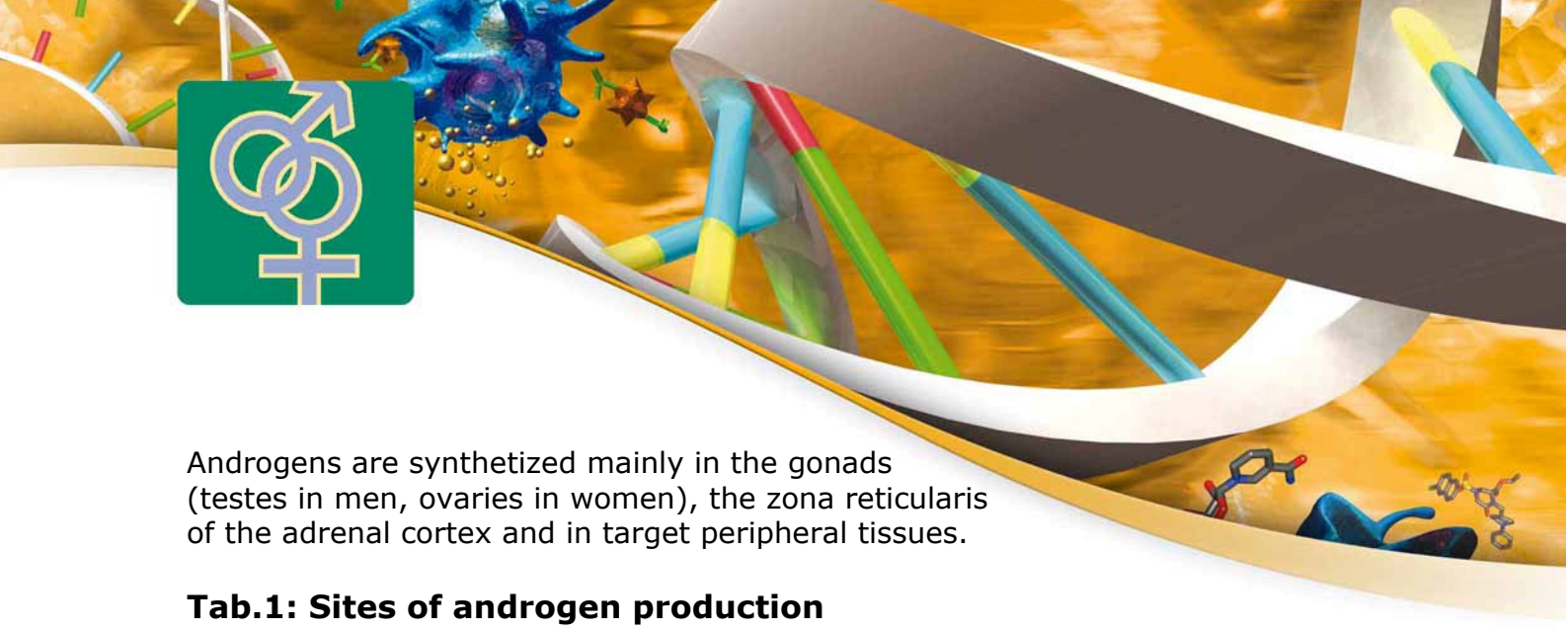


Biosynthesis

The synthesis of androgens begins with the mobilization of cholesterol from desposits of cholesterol esters stored in lipid droplets in cytoplasm. Cholesterol released from these droplets migrates to the inner mitochondrial membrane, where pregnenolone formation occurs by action of the cholesterol side-chain cleavage enzyme. The conversion of cholesterol to pregnenolone appears to be a rate-limiting step in androgen synthesis[14,15]. Androgen synthesis continues with the help of the enzymes 17α-hydroxylase, 3β-hydroxysteroid dehydrogenase (3β-HSD), 17β-hydroxysteroid dehydrogenase (17β-HSD), 17,20-lyase, 5α-reductase and 3α-hydroxysteroid dehydrogenase (Fig.4).

Fig.4: Biosynthesis of androgens (adrenal glands and testis) and related enzymes





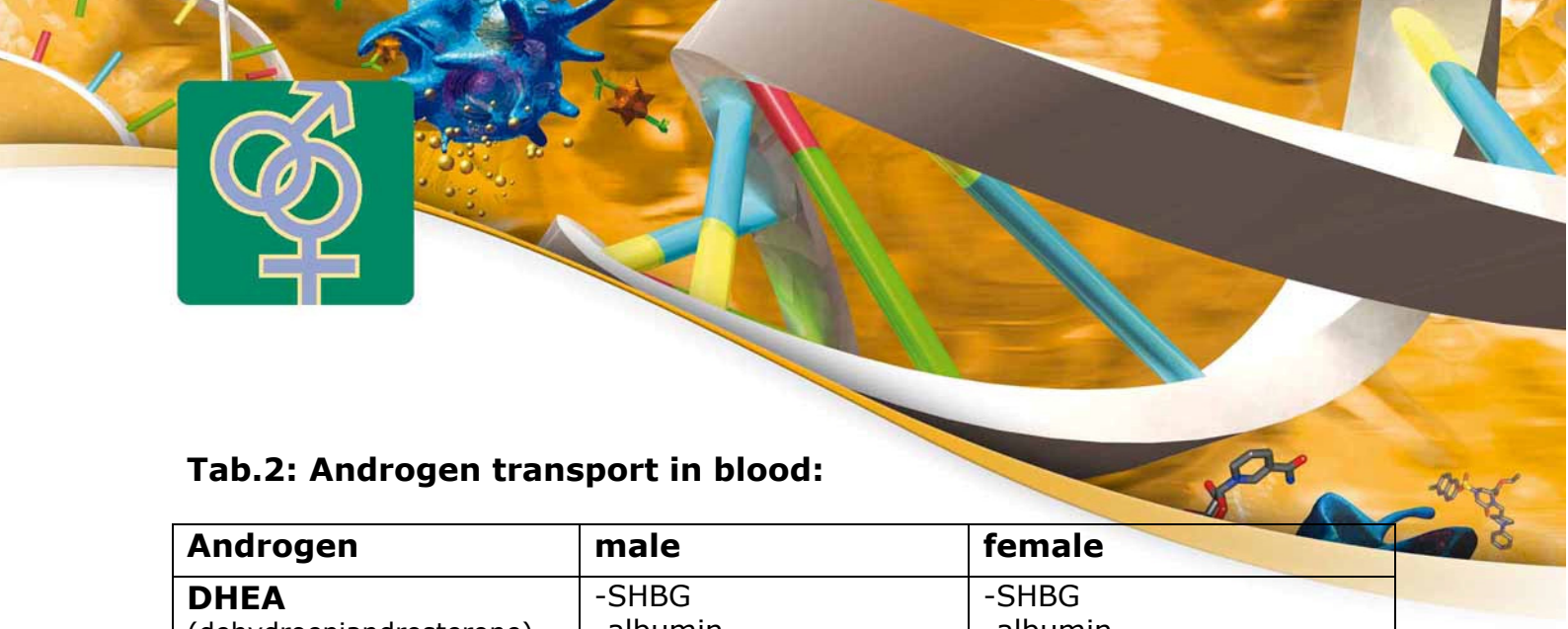
Androgens are synthetized mainly in the gonads (testes in men, ovaries in women), the zona reticularis of the adrenal cortex and in target peripheral tissues.

Tab.1: Sites of androgen production

Androgen	**male**	**female**
DHEA (dehydroepiandrosterone)	**-adrenal cortex** -testes (10–25%) -adipose tissues (minor) -brain (minor)	-**adrenal cortex** -ovary (minor) -adipose tissues (minor) -brain (minor)
DHEA-S (dehydroepiandrosterone sulfate)	**-adrenal cortex** -testes (5%)	-**adrenal cortex**
ASD (androstenedione)	**-testes** -adrenal cortex (2%)	-**adrenal cortex** (50%) **-ovary** (50%)
Testosterone	**-testes** -adrenal cortex (2%)	**-ovary** **-**adrenal cortex (minor) -peripheral tissues (minor)
DHT (ditydrotestosterone)	**-prostate gland** **-genital skin** **-hair follicles** -adrenal cortex -testes	**-peripheral tissues**
Androstanediol-glucuronide	**-liver** -skin	**-liver** -skin

Androgen transport in blood

Androgens can circulate in blood either in a free or bound to plasma proteins. The binding proteins include sex hormone-binding globuline (SHBG) and nonspecific proteins such as albumin. SHBG exhibits low capacity for androgens but binds to them with very high affinity, whereas albumin has high capacity but low affinity. A short summary is given in tab.2.



Tab.2: Androgen transport in blood:

Androgen	male	female
DHEA (dehydroepiandrosterone)	-SHBG -albumin	-SHBG -albumin
DHEA-S (dehydroepiandrosterone sulfate)	-albumin	-albumin
ASD (androstenedione)	-albumin	-albumin
Testosterone	-SHBG (44–65%) -albumin (33–55%) -free form (2–3%)[7]	-SHBG (66–78%) -albumin (20–30%) -free form (2–3%)[7]
DHT (ditydrotestosterone)	-SHBG -albimun -free (2–3%)	-SHBG -albumin -free (2–3%)
Androstanediol-glucuronide	-free	-free

Metabolism

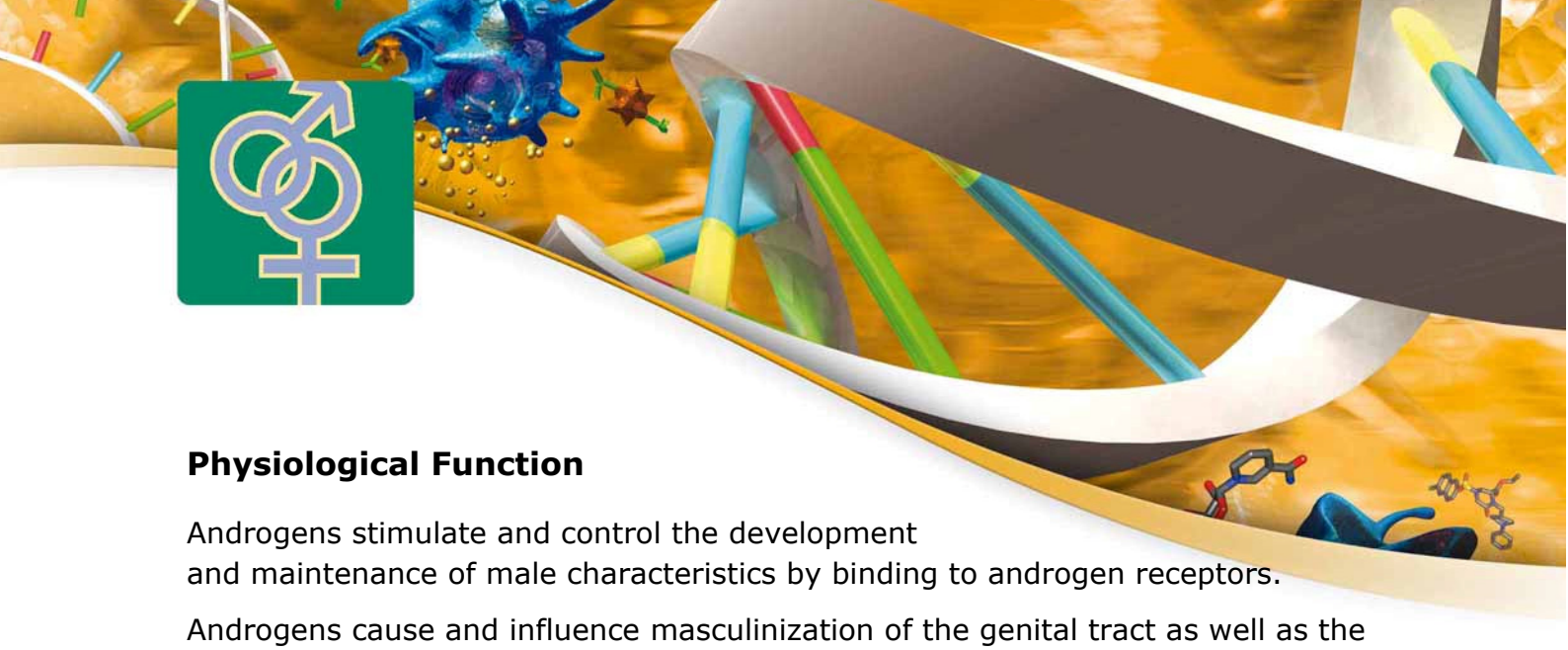
DHEA, DHEA-S and androstenedione serve mostly as precursors in testosterone and estrogen synthesis.

Testosterone serves as a precursor in the formation of two types of active metabolites. It may be converted to DHT by 5α-reductase; alternatively, both testosterone and androstenedione may be converted to estrogens by aromatase.

DHT is metabolized to 3α-androstanediol glucuronide–the end product of androgen degradation.

The main excretory metabolites of testosterone, androstenedione and DHEA are 17-ketosteroides (17-KSs) — androsterone, etiocholanolone, epiandrosterone — and polar metabolites — diols, triols and conjugates.

These metabolites are excreted primarily in urine (more than 90%), with roughly equal proportions of 17-KSs and diols, triols and conjugates.



Physiological Function

Androgens stimulate and control the development
and maintenance of male characteristics by binding to androgen receptors.

Androgens cause and influence masculinization of the genital tract as well as the development and maintenance of the male secondary sex characteristics[9,10]. These include facial hair, large muscles, deep voice and enlargement of the Adam's apple.Androgens also influence bone mass, hair loss, sex drive and male sexual performance.

Formation of testes and spermatogenesis

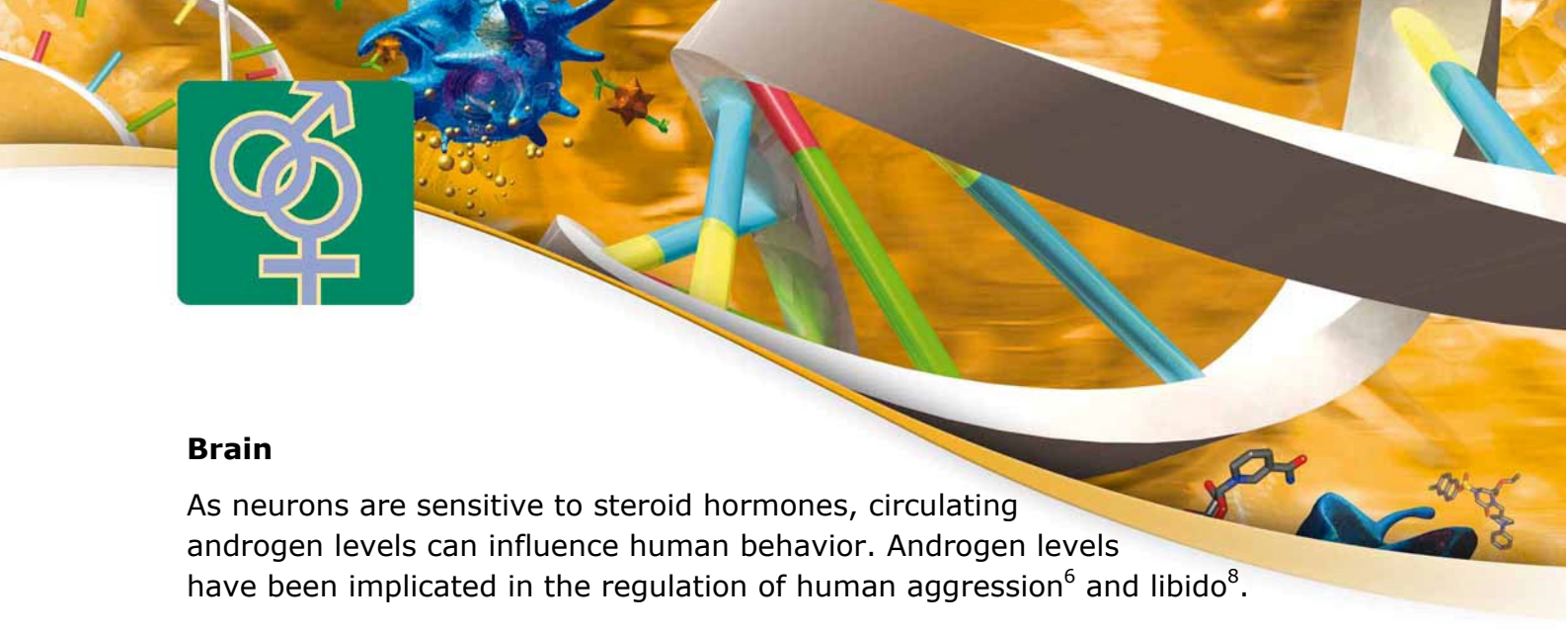
In mammalian fetal development, the gonads are initially capable of becoming either ovaries or testes[1]. In humans, starting at about week 4 the gonadal rudiments are present within the intermediate mesoderm adjacent to the developing kidneys. At about week 6, epithelial sex cords develop within the forming testes and incorporate germ cells as they migrate into the gonads. In males, certain Y chromosome genes, particularly SRY, control the development of the male phenotype, including conversion of the early bipotential gonads into testes.

During puberty, production of androgens, luteinizing hormone (LH) and follicle–stimulating hormone (FSH) increases. The sex cords hollow out, forming the seminiferous tubules and germ cells begin to differentiate into sperm. Throughout adulthood, androgens and FSH act cooperatively on Sertoli cells in the testes to support sperm production[2]. In the absence of high androgen levels in the testes, the seminiferous tubules can degenerate, resulting in infertility.

The androgens serve as paracrine hormones, which are required by Sertoli cells in order to support sperm production. They are also required for masculinization of the developing male fetus (including penis and scrotum formation).

Muscle mass

Males typically have more skeletal muscle mass than females. Androgens promote the enlargement of skeletal muscle cells and probably function in a coordinated manner by acting on several cell types within skeletal muscle tissue[4]. Higher androgen levels lead to increased androgen receptor expression. Fusion of myoblasts generates myotubes in a process linked to androgen receptor levels[5].



Brain

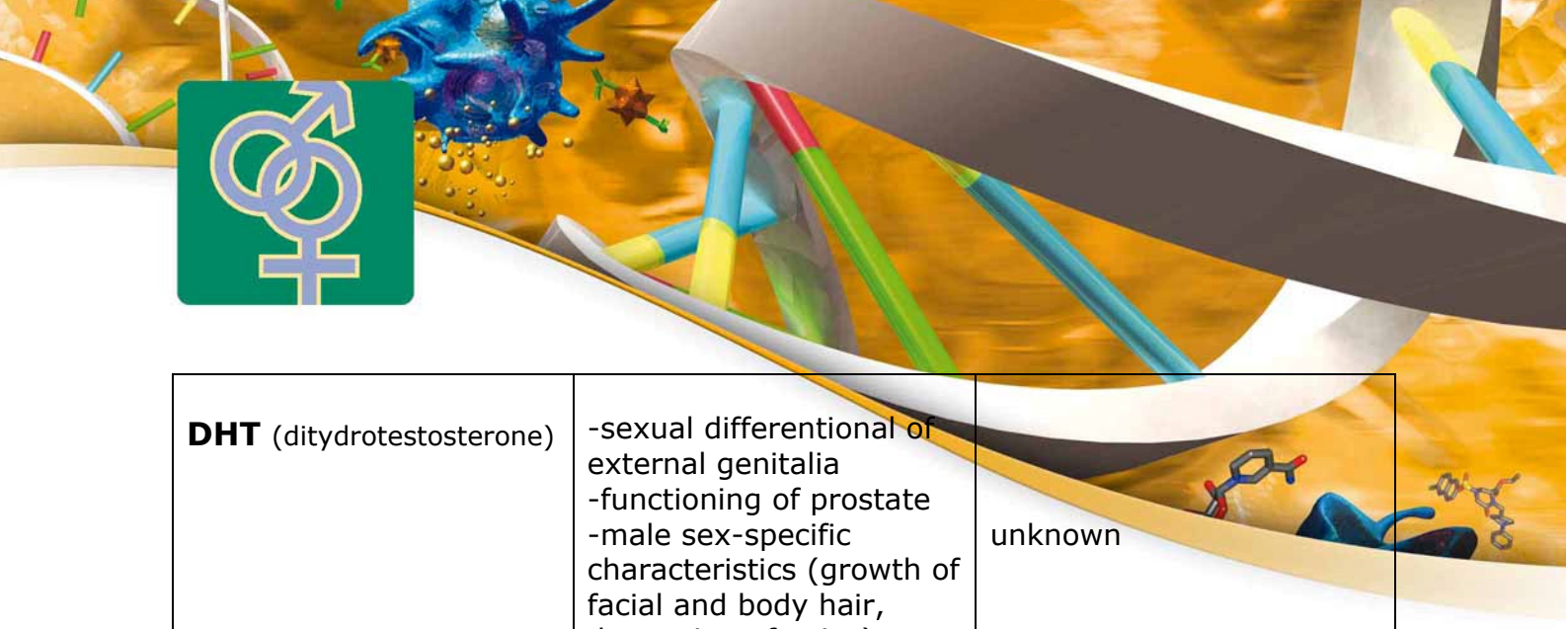
As neurons are sensitive to steroid hormones, circulating androgen levels can influence human behavior. Androgen levels have been implicated in the regulation of human aggression[6] and libido[8].

Inhibition of fat depositing

Males typically have less adipose tissue than females. Recent findings indicate that androgens inhibit the ability of certain fat cells to store lipids by blocking a signal transduction pathway that normally supports adipocyte function[3].

Tab.3: Summary of androgen physiological function:

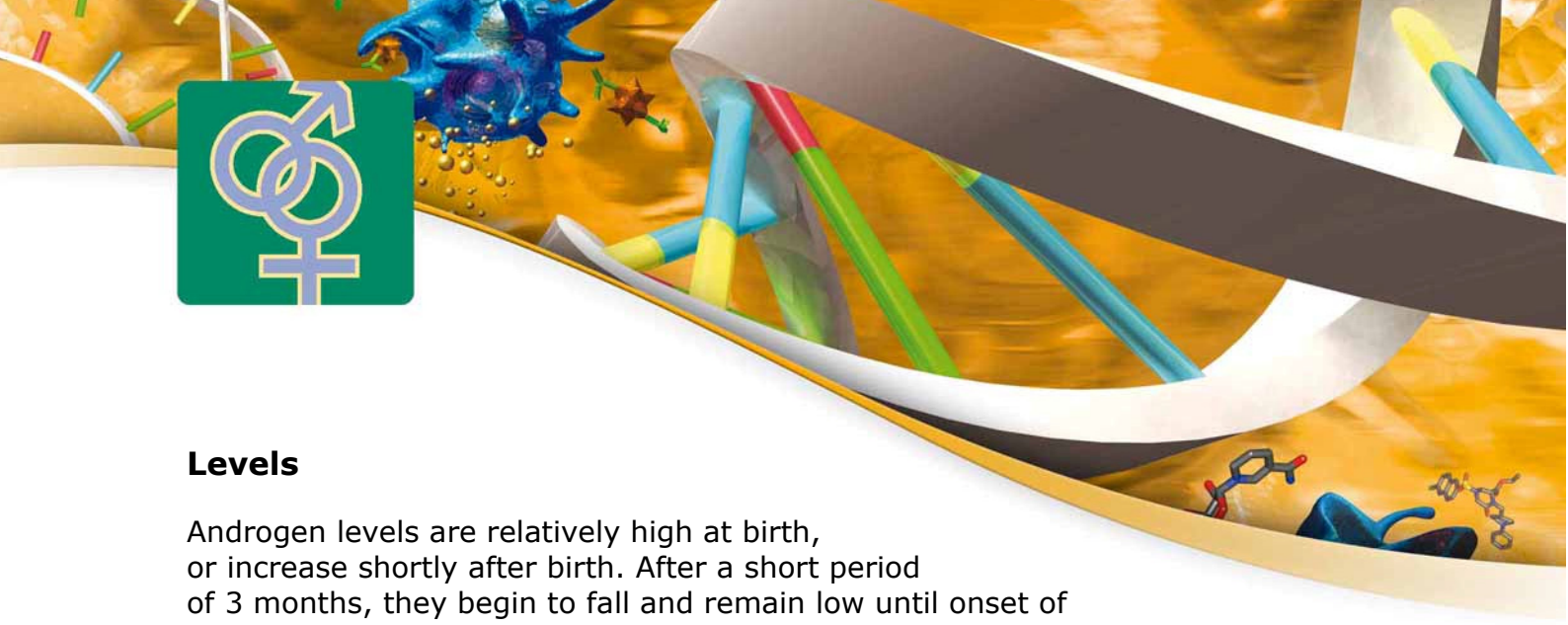
Androgen	**male**	**female**
DHEA (dehydroepiandrosterone)	not conclusively defined -prohormone for sex hormones[13](testosterone, estrogens) -anti-aging effects -increase immunity -others	not conclusively defined -prohormone for sex hormones[13] (estrogens, testosterone,) -anti-aging effects -increase immunity -others
DHEA-S (dehydroepiandrosterone sulfate)	-reservoir for DHEA	-reservoir for DHEA
ASD (androstenedione)	-prohormone for sex hormones (testosterone, estrogens)	-prohormone for sex hormones (estrogens, testosterone)
Testosterone	-development of male sex organs -development of sperm -functioning of prostate -muscle mass growth -stimulation of libido -prevention of osteoporosis -maitaining of Wolffian ducts in fetus	-estrogen precursor -stimulation of libido -muscle mass growth -prevention of osteoporosis



DHT (ditydrotestosterone)	-sexual differentional of external genitalia -functioning of prostate -male sex-specific characteristics (growth of facial and body hair, deepening of voice) -male-pattern baldness -mitigation of effects of estrogen -development of external genitalia in fetus	unknown
Androstanediol-glucuronide	-inactivation of androgens and urinary excretion	-inactivation of androgens and urinary excretion

Tab.4: Androgenic activity

Androgen	**Androgenic activity**
DHEA (dehydroepiandrosterone)	weak, 10% of testosterone[12]
DHEA-S (dehydroepiandrosterone sulfate)	weak[12]
ASD (androstenedione)	weak, less than 20% of testosterone[12]
Testosterone	strong androgen
DHT (ditydrotestosterone)	3 times more potent than testosterone
Androstanediol-glucuronide	weak



Levels

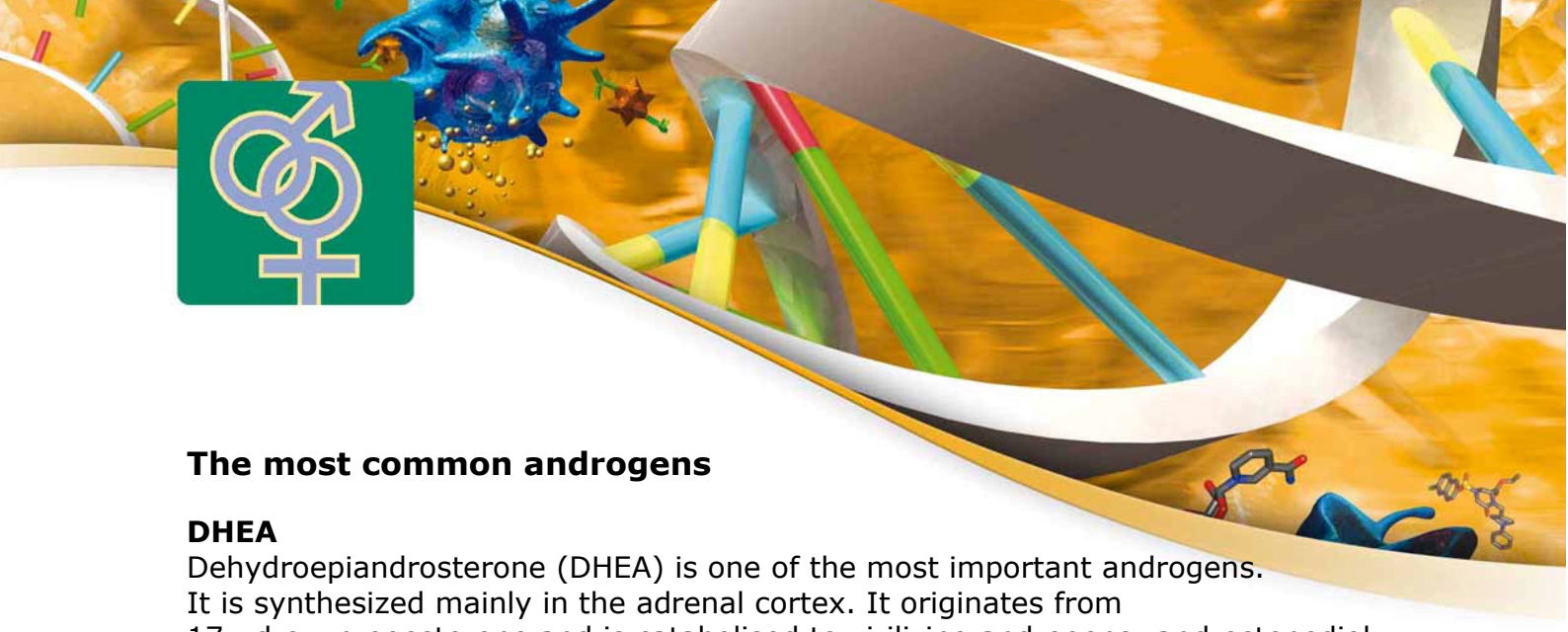
Androgen levels are relatively high at birth, or increase shortly after birth. After a short period of 3 months, they begin to fall and remain low until onset of adrenarche or puberty. Maximal levels are typically reached between ages 20–30. After age 50–60, androgen levels decrease rapidly.

DHEA, DHEA-S and ASD levels are similar in both men and women. Testosterone, DHT and androstanediol glucuronide levels are much lower in women than in men.
Androgen levels may be influenced by SHBG levels, by various disorders, pregnancy, and androgen administration.

For each assay, the relevant reference values are shown in the appropriate Instructions for Use (IFU).

Tab.5: Typical androgen levels in adult males and females[9]:

Androgen	**male**	**female**
DHEA (dehydroepiandrosterone)	1.80–12.5 ng/mL	1.30–9.80 ng/mL
DHEA-S (dehydroepiandrosterone sulfate)	1,250–6,190 ng/mL	290–7,810 ng/mL
ASD (androstenedione)	0.75–2.05 ng/mL	0.85–2.75 ng/mL
Testosterone	2.80–11.0 ng/mL	0.15–0.70 ng/mL
DHT (ditydrotestosterone)	0.30–0.85 ng/mL	0.04–0.22 ng/mL
Androstanediol-glucuronde	2.60–15.0 ng/mL	0.60–3.00 ng/mL



The most common androgens

DHEA

Dehydroepiandrosterone (DHEA) is one of the most important androgens. It is synthesized mainly in the adrenal cortex. It originates from 17-ydroxyprogesterone and is catabolised to virilizing androgens: androstenediol, testosterone and dihydrotestosterone. DHEA levels exhibit a circadian rhythm, reaching a maximum in the morning. The menstrual cycle does not substantially affect DHEA production. DHEA has a relatively low affinity for albumin and SHBG, and is only weakly androgenic.

Diagnostic information

Elevated DHEA levels:

Adrenogenital syndrome due to 3β-dehydrogenase, 21-hydroxylase, and 11β-hydroxylase deficiency; hirsutism; polycystic ovary syndrome, virilizing adrenal tumors; Cushing's disease; ectopic ACTH-producing tumors.

Decreased DHEA levels:

Old age, hyperlipidemia, psychosis, psoriasis.

DHEA-S

Dehydroepiandrosterone sulfate (DHEA-S) originates almost exclusively in the adrenals, although some may be derived from the testes (None is produced by the ovaries.) DHEA-S is weakly androgenic but is metabolized in peripheral tissues to testosterone and dihydrotestosterone. DHEA-S plasma levels are 1000 times higher than those of DHEA. Unlike DHEA, DHEA-S does not exhibit marked diurnal variation and has a low clearance rate. DHEA-S has a relatively high affinity for albumin and does not circulate bound to SHBG.

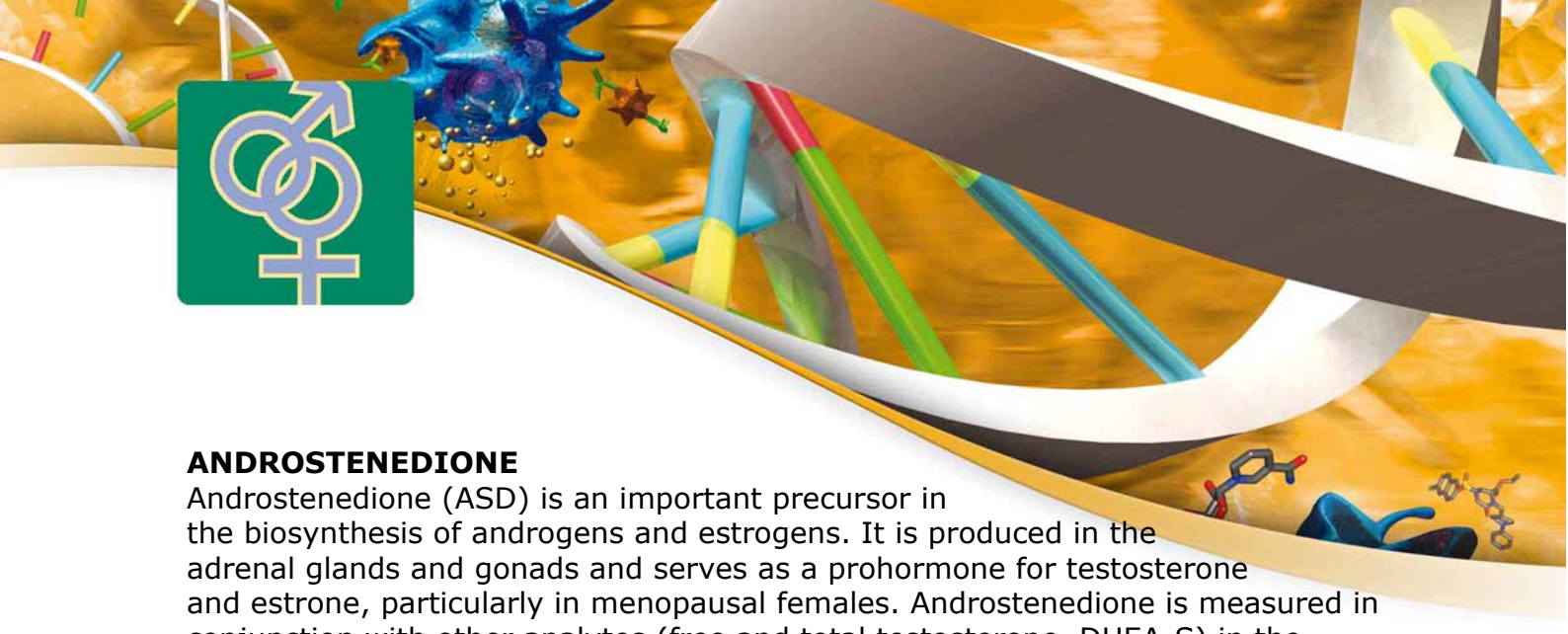
Diagnostic information

Elevated DHEA-S levels:

Hirsutism in females, acne, congenital adrenal hyperplasia, adrenal cortex tumors (values higher in adrenal carcinomas than in adrenal adenomas), Cushing's disease, ectopic ACTH-producing tumors, polycystic ovary syndrome, precocious puberty.

Decreased DHEA-S levels:

Adrenal insufficiency (primary or secondary).



ANDROSTENEDIONE

Androstenedione (ASD) is an important precursor in the biosynthesis of androgens and estrogens. It is produced in the adrenal glands and gonads and serves as a prohormone for testosterone and estrone, particularly in menopausal females. Androstenedione is measured in conjunction with other analytes (free and total testosterone, DHEA-S) in the evaluation and management of various androgen disorders.

Diagnostic information

Elevated ASD levels:

Polycystic ovary syndrome (some cases), hirsutism (some cases), congenital adrenal hyperplasia, Cushing's disease, ectopic ACTH-producing tumors, hyperplasia of ovarian stroma or ovarian tumors, osteoporosis in females.

Decreased ASD levels:

Sickle cell anemia, adrenal failure, ovarian failure.

TOTAL and FREE TESTOSTERONE

Testosterone is the main androgen secreted by the Leydig cells of the testes. A small amount is also derived from peripheral conversion of androstenedione. Testosterone circulates in three forms: free (non-protein-bound), weakly bound to albumin, and tightly bound to SHBG. Free and albumin-bound testosterone is biologically active, thus free testosterone level may reflect testosterone bioactivity better than total testosterone, which is strongly affected by SHBG concentration. In situations in which SHBG levels are elevated (e.g., hyperthyroidism, hyperestrogenic states such as pregnancy or oral contraceptive use, administration of antiepileptic drugs) or decreased (e.g., hypothyroidism, androgen excess, obesity), measurement of free testosterone may be more appropriate than measurements of total testosterone.

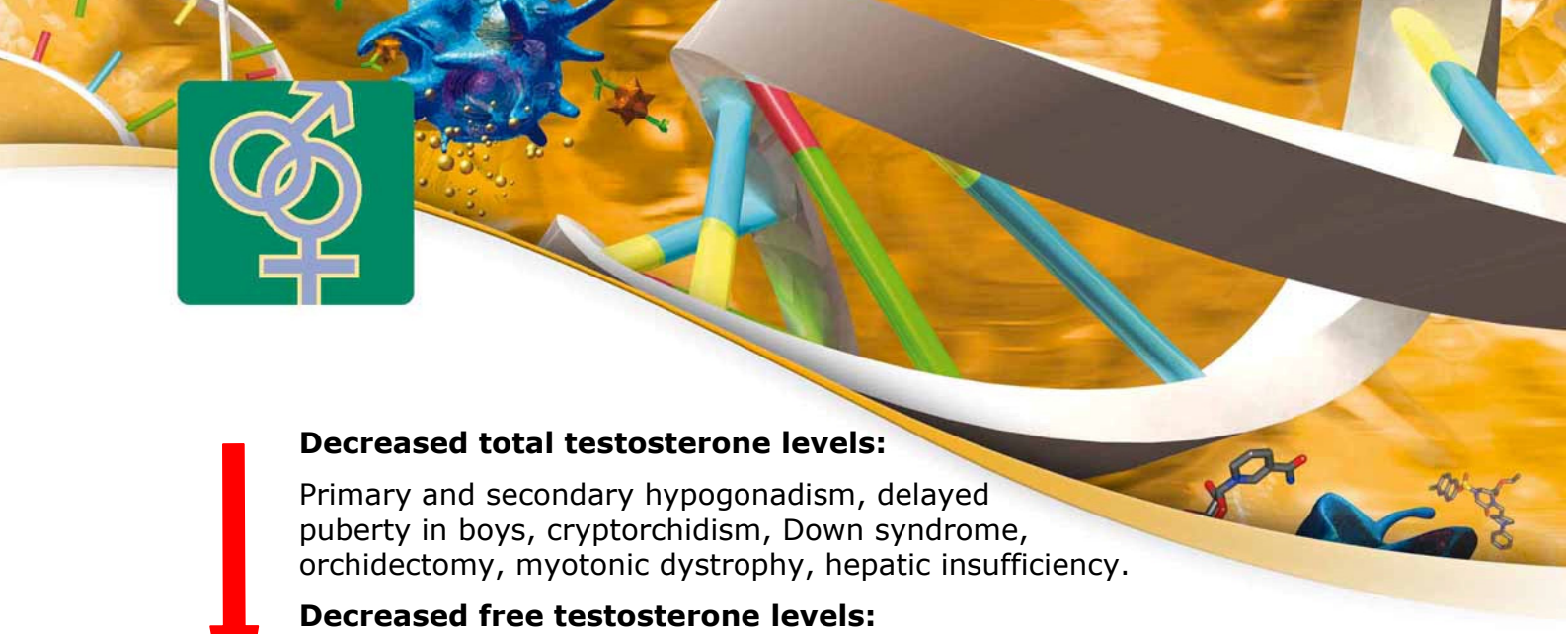
Diagnostic information

Elevated total testosterone levels:

Idiopathic sexual precocity, adrenal hyperplasia in boys, some adrenocortical tumors, extragonadal gonadotropin-producing tumors in men, trophoblastic disease during pregnancy, testicular feminization, idiophatic hirsutism, virilizing ovarian tumors, arrhenoblastoma, hilar cell tumors, virilizing luteoma.

Elevated free testosterone levels:

Hirsutism, virilizing adrenal tumors, polycystic ovary syndrome, and androgen resistance.



Decreased total testosterone levels:

Primary and secondary hypogonadism, delayed puberty in boys, cryptorchidism, Down syndrome, orchidectomy, myotonic dystrophy, hepatic insufficiency.

Decreased free testosterone levels:

Hypogonadism, P-450c17 enzyme deficiency. An increase in SHBG concentration and a decrease in free testosterone levels are reported in elderly men.

DIHYDROTESTOSTERONE

DHT is a powerful androgen formed in target tissues by peripheral conversion of androstenedione and testosterone by a cellular 5α-reductase. A small amount of DHT produced in target tissues is extracted into circulation, most of it being metabolised into 3α-androstanediol glucuronide, the final product of peripheral androgen metabolism. Serum concentration of DHT is closely related to testosterone concentration but is lower. There is a decrease in the ratio of DHT to testosterone throughout pregnancy.

Diagnostic information

Elevated DHT levels:

Hirsutism, male pattern baldness, benign prostatic hyperplasia, prostate cancer

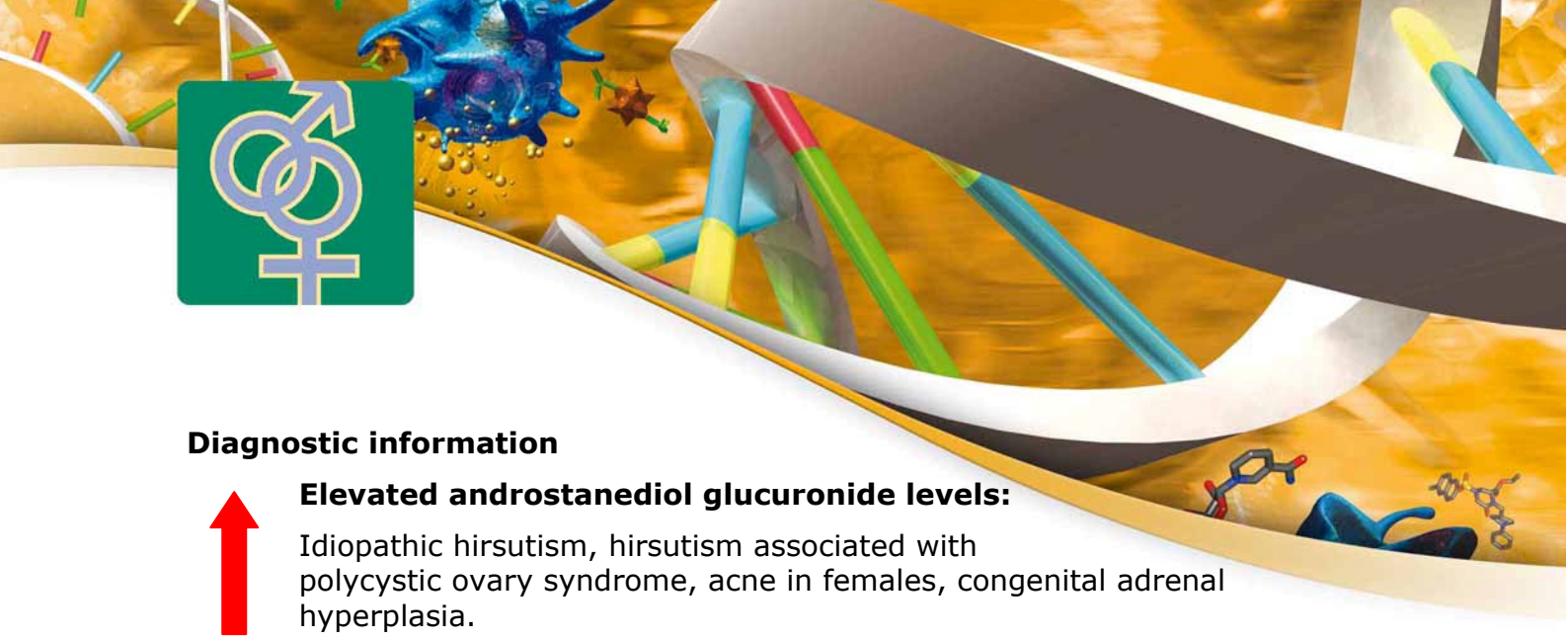
Decreased DHT levels:

5α-reductase deficiency, hypogonadism.

ANDROSTANEDIOL GLUCURONIDE

Androstanediol glucuronide, also named 3α-diol glucuronide, is the product of intracellular reduction of DHT, and is in fact a major metabolite of DHT. In addition, a significant proportion is derived from DHEA-S and androstenedione. Measurement of 3α-diol glucuronide is an indirect way of testing 5α-reductase activity and is a marker of peripheral androgen conversion[11]. It is useful in the differential diagnosis of hirsutism, especially when levels of circulating androgens (testosterone, free testosterone, and dihydrotestosterone) are within normal limits.

The determination of androstanediol glucuronide is also useful for monitoring of clinical response to hirsutism treatment.



Diagnostic information

Elevated androstanediol glucuronide levels:

Idiopathic hirsutism, hirsutism associated with polycystic ovary syndrome, acne in females, congenital adrenal hyperplasia.

Decreased androstanediol glucuronide levels:

Androgen action disorders in men (e.g., male pseudohermaphroditism).

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