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Mechanism of testosterone production

Introduction

Testosterone is the primary male hormone responsible for regulating sex differentiation, producing male sex characteristics, spermatogenesis and fertility. Testosterone's effects are first seen in the fetus. During the first 6 weeks of development, the reproductive tissues of males and females are identical. At around week 7 in utero, the SRY (sex-related gene on the Y chromosome) initiates the development of the testicles. Sertoli cells from the testis cords (fetal testicles) eventually develop into seminiferous tubules. Sertoli cells produce a Mullerian-inhibiting substance (MIS), which leads to the regression of the fallopian tubes, uterus, and upper segment of the vagina (Mullerian structures normally present in females). Fetal Leydig cells and endothelial cells migrate into the gonad and produce testosterone, which supports the differentiation of the Wolffian duct (paramesonephric duct) structures that go on to become the male urogenital tract. Testosterone also gets converted to dihydrotestosterone (DHT) in the periphery (discussed below) and induces the formation of the prostate and male external genitalia. Testosterone is also responsible for testicular descent through the inguinal canal, which occurs in the last 2 months of fetal development. When an embryo lacks a Y chromosome and thus the SRY gene, ovaries develop. Fetal ovaries do not produce adequate amounts of testosterone, thus the Wolffian ducts do not

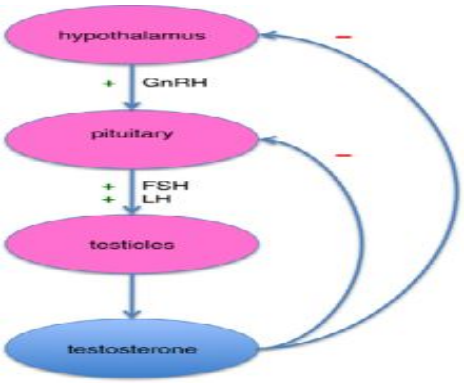
develop. There is also an absence of MIS in these individuals, leading to the development of the Mullerian ducts and female reproductive structures.

Mechanism of testosterone production

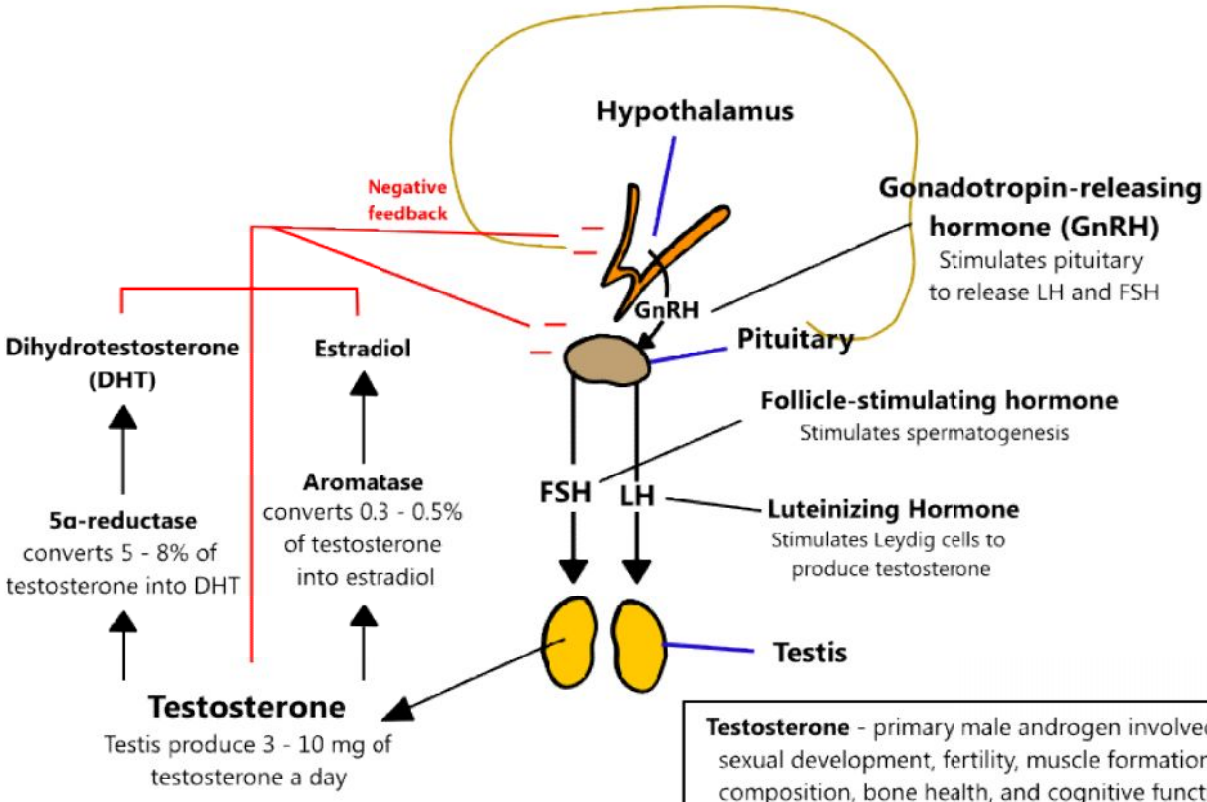
In puberty, the hypothalamic-pituitary-gonadal axis takes a major role in regulating testosterone levels and gonadal function. The hypothalamus secretes GnRH, which travels down the hypothalamo-hypophyseal portal system to the anterior pituitary, which secretes luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH and FSH are two gonadotropic hormones which travel through the blood and act on receptors in the gonads. LH in particular acts on the Leydig cells to increase testosterone production. Testosterone limits its own secretion via negative feedback. High levels of testosterone in the blood feedback to the hypothalamus to suppress the secretion of GnRH and also feedback to the anterior pituitary, making it less responsive to GnRH stimuli. Throughout the reproductive life of males, the hypothalamus releases GnRH in pulses every 1 to 3 hours. Despite this pulsatile release, however, average plasma levels of FSH and LH remain fairly constant from the start of puberty, where levels spike, to the third decade of life, where levels peak and slowly begin to decline. Prior to puberty, testosterone levels are low, reflecting the low secretion of GnRH and gonadotropins. Changes in neuronal input to the hypothalamus and brain activity during puberty, cause a dramatic rise in GnRH secretion.

Leydig cells in the testes function to turn cholesterol into testosterone. LH regulates the initial step in this process. Two important intermediates in this process are dehydroepiandrosterone (DHEA) and androstenedione. Androstenedione is converted to

testosterone by the enzyme 17-beta-hydroxysteroid dehydrogenase. The majority of testosterone is bound to plasma proteins such as sex-hormone-binding-globulin and albumin. This majority supply of protein-bound testosterone acts as a surplus of testosterone hormone for the body. The small amounts of free testosterone in the blood act at the level of the tissues, primarily the seminal vesicles, bone, muscle, and prostate gland. At the cellular level, testosterone gets converted to dihydrotestosterone by the enzyme 5-alpha-reductase. Testosterone and dihydrotestosterone can bind to cell receptors and regulate protein expression. Both men and women also produce weak acting androgens in the zona reticularis of the adrenal glands. These weak-acting androgens are known as dehydroepiandrosterone and androstenedione. They bind to testosterone receptors with weaker affinity but can also be converted to testosterone in the peripheral tissues if produced at high amounts.



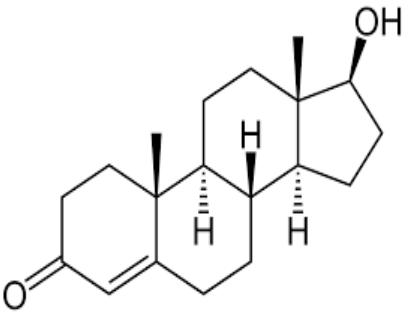
Feedback inhibition of testosterone production



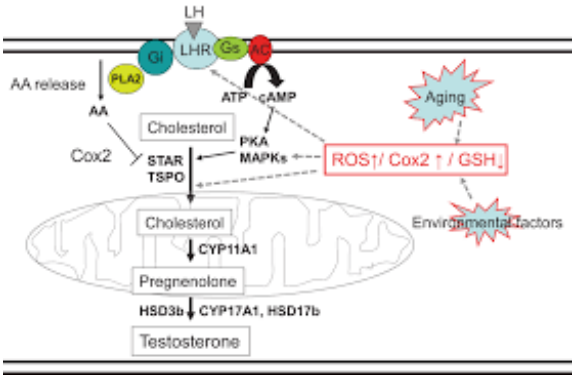
Testosterone - primary male androgen involved in sexual development, fertility, muscle formation, body composition, bone health, and cognitive function

Dihydrotestosterone (DHT) - a more potent androgen involved in hair follicles (hair loss), prostate development, sebum production, and external genitalia development

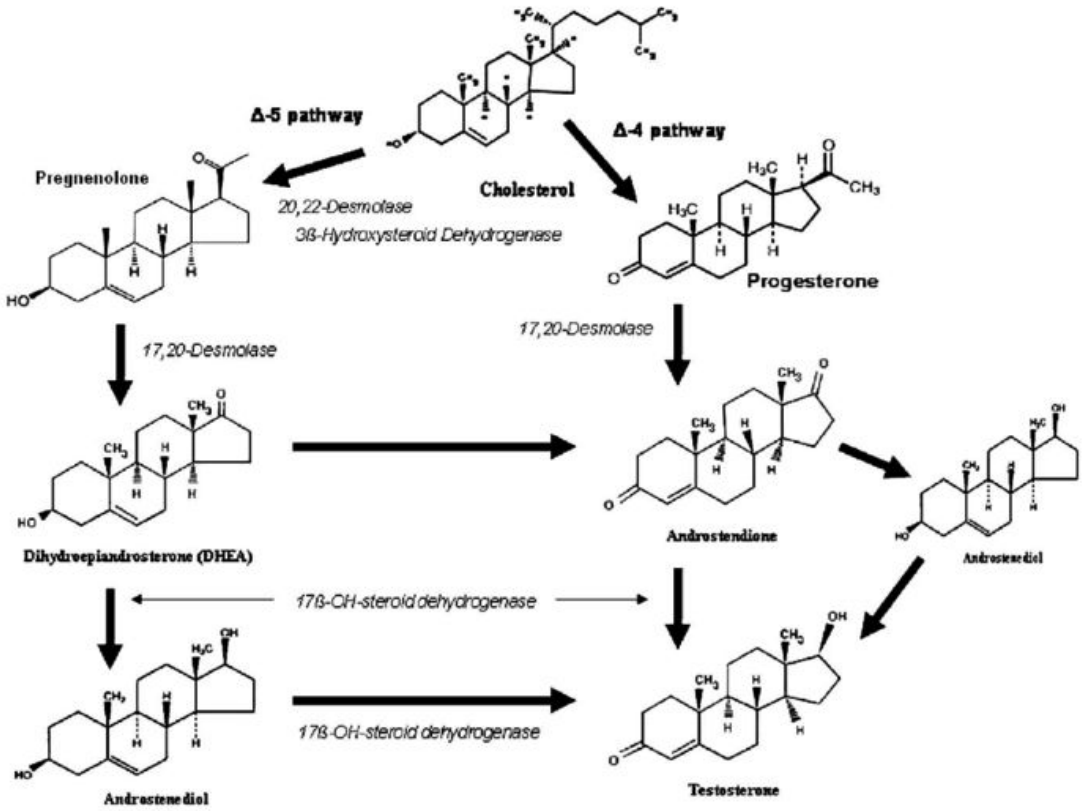
Estradiol - small amount of testosterone is converted into the female hormone estradiol. Estradiol plays an important role in bone health, cognitive function, and plasma lipids



Chemical structure of testosterone



Environmental factor affect the production of testosterone


Δ-5 pathway
Δ-4 pathway
Cholesterol
Pregnenolone
20,22-Desmolase
3ß-Hydroxysteroid Dehydrogenase
Progesterone
17,20-Desmolase
17,20-Desmolase
Dihydroepiandrosterone (DHEA)
Androstendione
Androstenediol
17ß-OH-steroid dehydrogenase
17ß-OH-steroid dehydrogenase
Androstenediol
Testosterone