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SYNTHESIS OF STEROID HORMONES AND ABNORMALITIES

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Abstract : Steroid hormones, many of which are of great clinical significance, are synthesized in the adrenal cortex, gonads, and placenta. Both the mitochondria and the smooth endoplasmic reticulum participate in the synthesis of steroid hormones. They are synthesized on demand as precursors because they are lipophilic and cannot be stored in vesicles, where they would diffuse easily. Once the parent cell is stimulated, the steroid hormone precursors are converted into the mature hormones and diffuse out of the cell via simple diffusion. Steroid hormones are insoluble in plasma and other body fluids because they are all constructed from cholesterol. Steroids are given a longer half-life and more widespread distribution by binding to transport proteins. The adrenal medulla and adrenal cortex make up the adrenal glands. There are three main anatomical regions in the adrenal cortex: the zona glomerulosa, which is responsible for the production of aldosterone; the zona fasciculata; and the zona reticularis, which is responsible for the production of cortisol and adrenal androgens. The adrenal cortex secretes over 30 different steroids, which fall into three functional groups: mineralocorticoids, glucocorticoids, and androgens. Cortisol, 11-deoxycortisol, aldosterone, corticosterone, and 11-deoxycortisol are the adrenal gland steroids that are produced almost exclusively in these glands. The adrenal glands and the gonads produce the majority of the other steroid hormones, including the estrogens.

IndexTerms **- Aromatase, 17 alpha(α)-hydroxylase, 21-b hydroxylase, 11-b hydroxylase, Congenital adrenal hyperplasia & Penis at 12 syndrome.**

INTRODUCTION

Cholesterol is essential for cell membrane structure and function, and it is also used as a precursor in the biosynthesis of steroid hormones, vitamin D, and bile acids. Cholesterol is essential for regulating cellular function in addition to its role in structurally providing stability and fluidity. Cholesterol has a very unusual structure consisting of 27 carbon atoms, including a hydrocarbon tail, four hydrocarbon rings in a central sterol nucleus, and a hydroxyl group. All steroid hormones share a common structural component—a central sterol nucleus or ring. The central ring and hydrocarbon tail are both non-polar, so they do not dissolve in water. In order to be transported by the bloodstream, cholesterol (a lipid) must be packaged with apoproteins (a protein).

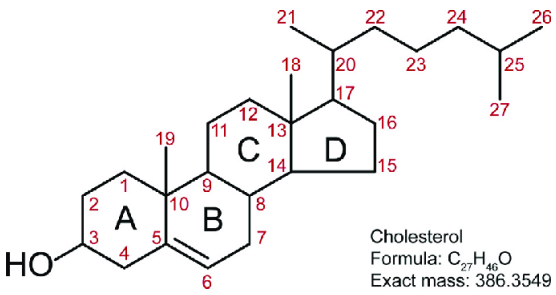
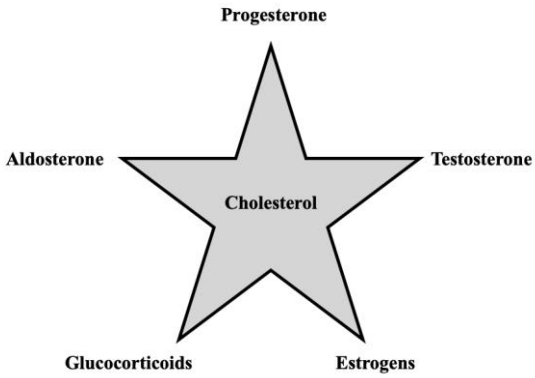
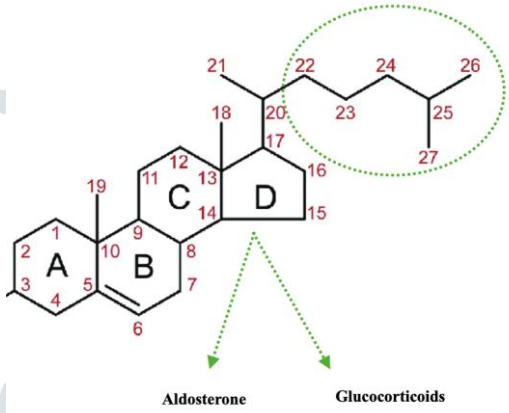


Figure 1: Structure of Cholesterol

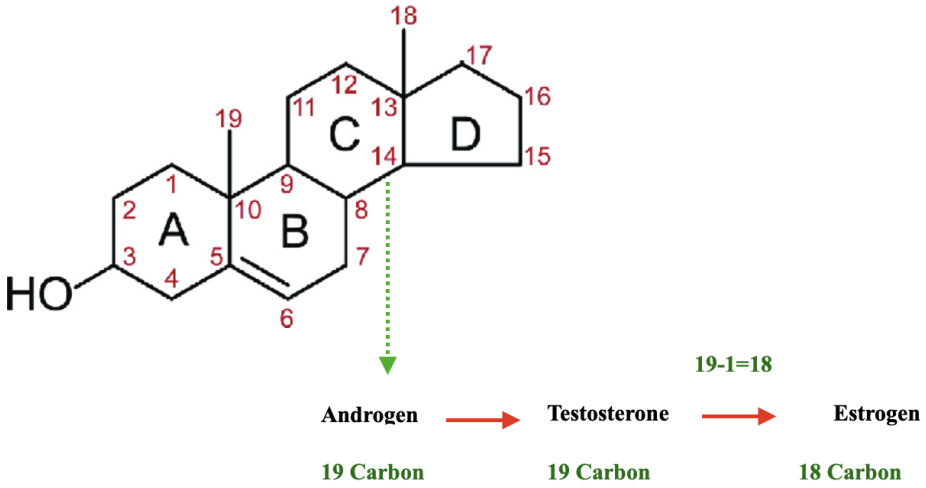
Steroidogenesis begins when cholesterol binds to the mitochondrial enzyme P450scc (the cholesterol side-chain cleavage enzyme). Most of the cholesterol our bodies make is processed in the liver to create pregnenolone, a biosynthetic precursor to nearly all of our hormones. Cholesterol is the source of bile, but it isn't a hormone. Further conversion of pregnenolone can lead to a variety of forms, including:



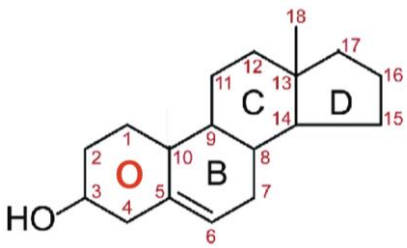
A total of 21 molecules are required for conversion to either aldosterone or glucocorticoids (via the removal of carbons 22–27).



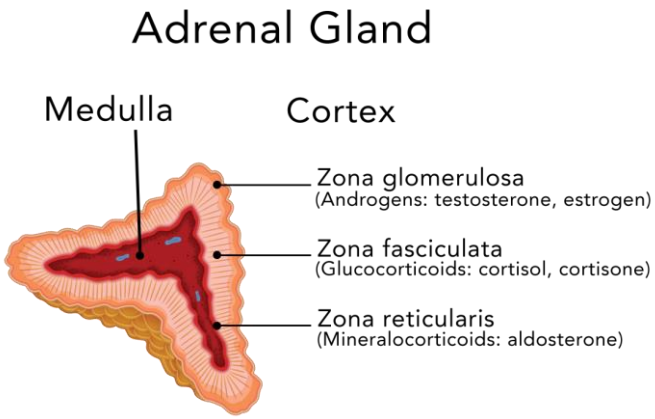
Androgen formation necessitates the addition of 19 molecules (via the removal of carbons 20–27). The process of converting androgen to testosterone begins. Aromatase is an enzyme responsible for the conversion of androgen to estrogen.



Aromatase is an enzyme that converts androgen to estrogen via a different pathway. Aromatase has the ability to convert the A-rings in cholesterol to the O-rings (Aromatase ring).



How does the adrenal gland produce steroid hormones?



Steroid hormones produced by the adrenal glands are made primarily from plasma cholesterol (some cholesterol is synthesized in situ from acetyl-CoA). Aldosterone is produced when the adrenal zona glomerulosa is stimulated by angiotensin II; when the adrenal zona fasciculata is stimulated by ACTH (adrenocorticotropic hormone), more glucocorticoids and fewer androgen hormones are produced; and when the adrenal zona reticularis is stimulated, primarily androgen hormones and some mineralocorticoids are produced.

Synthesis of steroids hormones in adrenal gland

Mitochondrion uses an enzyme called desmolase, which is controlled by ACTH, to break up the carbon molecules. The remaining carbon molecules are called pregnenolone. Pregnenolone is then converted into progesterone. Progestin, or progesterone, can be converted into aldosterone, testosterone, and estrogen. Once hormones are created, they will no longer be stored in vesicles. Hormones do not dissolve in plasma water because they are composed of cholesterol. Hormones will be transported to target tissues via plasma proteins. Steroid hormone receptors can be found in either the cytoplasm or the nucleoplasm. Eventually, the liver deactivates steroid hormones. The anti-fungal medication ketoconazole can inhibit the activity of desmolase.

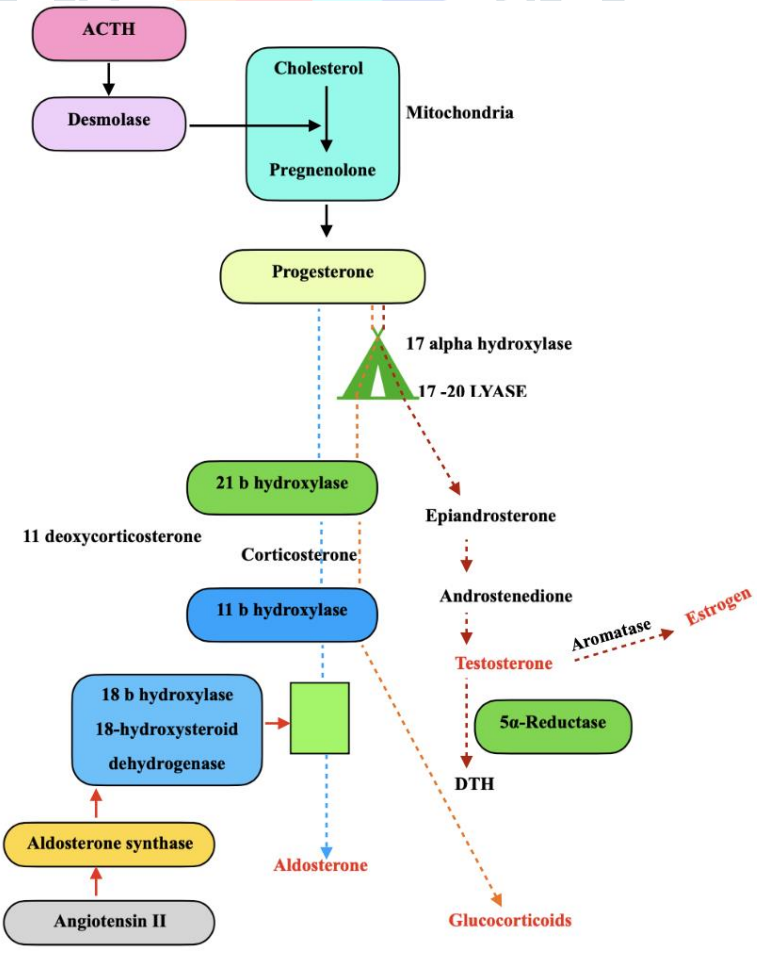


Figure 2:Major adrenal steroid synthesis pathways

1. Aldosterone biosynthesis

Mineralocorticoid synthesis takes place in the zona glomerulosa (ZG) and requires three enzymes: 1. 3-hydroxysteroid dehydrogenase type 2 (HSD3B2), which catalyzes the irreversible conversion of the hydroxyl group to a keto group on carbon 3 and the simultaneous isomerization of the double bond from the 5 to the 4 position; 2. 21-hydroxylase (CYP21A2, P450c21), which converts progesterone to 11-deoxycosticosterone; and 3. aldosterone synthase. The 18-aldehyde group, from which the term "aldosterone" is derived, forms an intramolecular cyclic hemiacetal through the use of the 11-hydroxyl group, with the loss of water. The ZG is optimized for aldosterone synthesis: it is the only zone with CYP11B2 and has low levels of 17-hydroxylase/17,20-lyase (CYP17A1, P450c17), an enzyme that directs steroid substrates to cortisol and androgen synthesis. Angiotensin II and a high extracellular potassium concentration are the primary stimulators of aldosterone synthesis, which is mediated by an increase in intracellular calcium.

2. Glucocorticoid biosynthesis

In response to adrenocorticotropin (ACTH), the zona fasciculata (ZF) produces cortisol. CYP17A1 catalyzes the 17-hydroxylation of pregnenolone and progesterone with roughly equivalent efficiency, resulting in the production of cortisol. Additionally, CYP17A1 cleaves the C17-C20 bond of 17-hydroxypregnenolone and, to a lesser extent, 17-hydroxyprogesterone (17OHP), resulting in the formation of 19-carbon (C19) steroids. Both reactions occur at the same active site, but are regulated differently, as described below. 17-hydroxysteroids are converted to 11-deoxycortisol by the actions of HDS3B2 and CYP21A2, enzymes that perform similar reactions to those on the mineralocorticoid pathway. Cortisol synthesis is completed by 11-hydroxylase (CYP11B1, P450c11), an enzyme closely related to CYP11B2.

3. Adrenal androgen biosynthesis

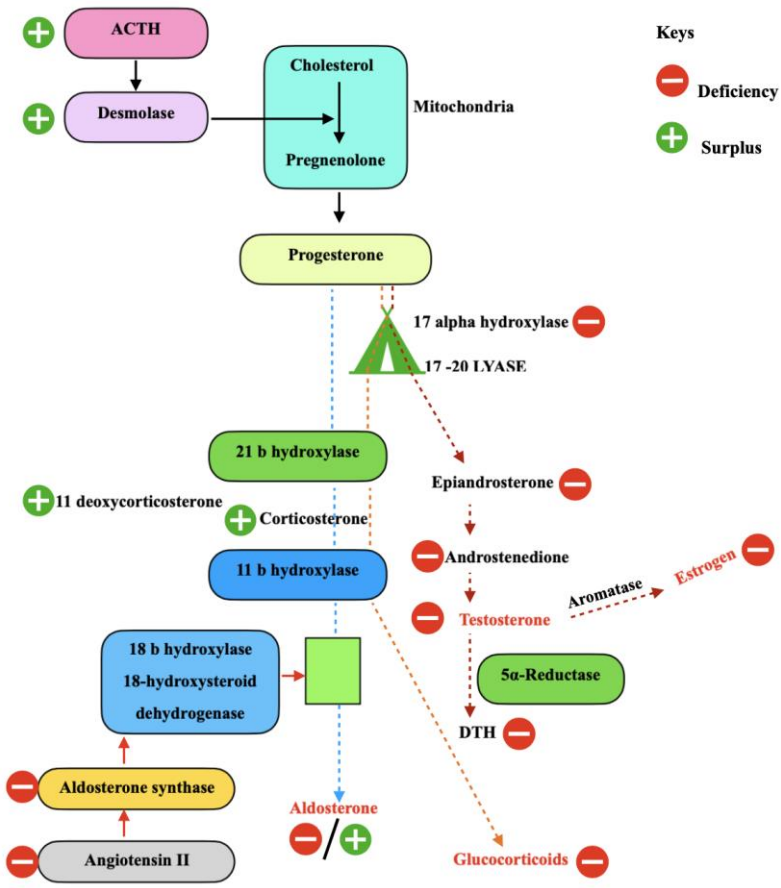
In the zona reticularis, adrenal C19 steroid hormones are produced (ZR). The two most abundant adrenal steroids are dehydroepiandrosterone (DHEA) and its sulphate (DHEAS). The only enzyme required for the synthesis of DHEA from pregnenolone and androstenedione (AD) from progesterone is CYP17A1. While CYP17A1 is present in both ZF and ZR, its 17,20-lyase reaction is approximately tenfold enhanced by the ZR-exclusive cofactor cytochrome b5 (CYB5A). DHEA is conjugated by SULT2A1 to DHEAS, an important regulator of adrenal androgen synthesis. AD catalyzes the synthesis of small amounts of testosterone by 17-hydroxysteroid dehydrogenase type 5 (17HSD5, AKR1C3).

ABNORMALITIES IN THE SYNTHESIS OF STEROID HORMONES

1. Deficiency of 17 alpha(α)-hydroxylase

A deficiency in 17 alpha-hydroxylase can reduce sex hormones and glucocorticoids. Reduced glucocorticoids cannot provide a negative feedback system to the anterior pituitary, resulting in an increase in ACTH production. Increased ACTH can overstimulate desmolase, resulting in elevated aldosterone levels.

Pathway of 17 alpha(α)-hydroxylase deficiency



Physiological changes in 17 alpha(α)-hydroxylase deficiency

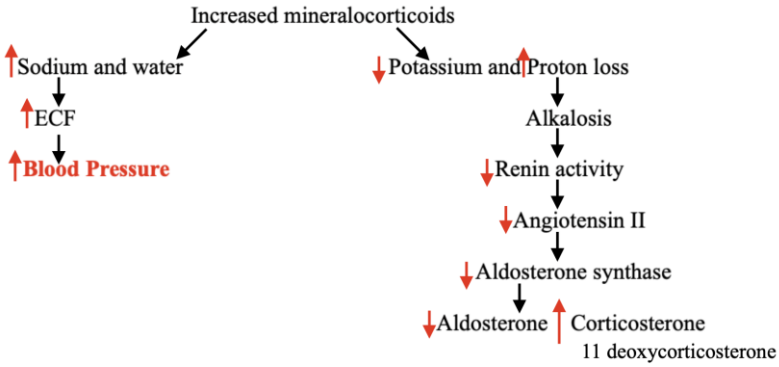
I. Decreased sex hormones

- **XY** - Female like genitals
- **XX** - Secondary sex traits do not emerge.

II. Decreased glucocorticoids (hypoglycemia)

- Increased ACTH

III. Increased mineralocorticoids

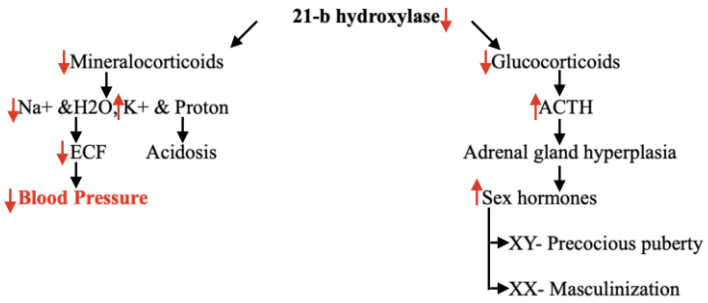


2. Congenital adrenal hyperplasia (Adrenal genital syndrome)

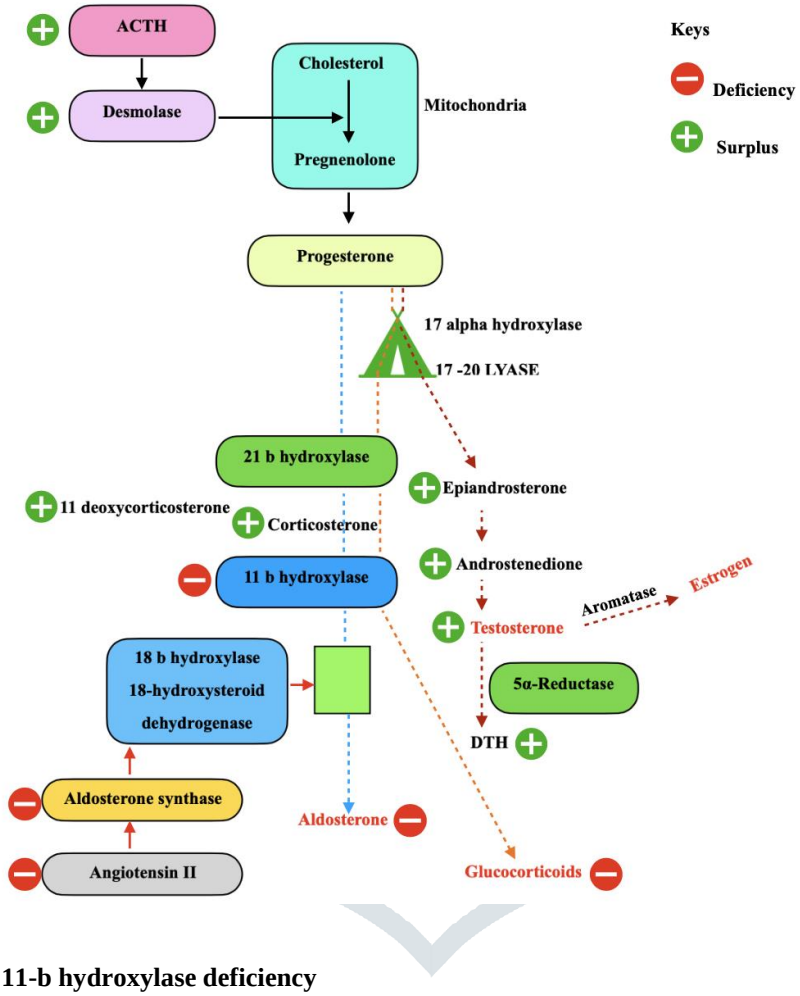
CAH, or congenital adrenal hyperplasia, is a term used to describe a spectrum of conditions caused by improper steroidogenesis during development. There are five primary phases, all mediated by enzymes, in the manufacture of cortisol in the adrenal cortex's zona fasciculata. If any of these enzymes are missing, CAH will develop. The adrenal cortex becomes hyper plastic and over-secretes the precursors of the enzymatic deficiency when cortisol production is impaired, leading to prolonged increases in ACTH via the negative feedback loop. When there is a breakdown in the production of adrenal cortisol at any stage, the result is an abnormal mixture of increased precursors and inadequate products. Lack of the enzyme 21-b hydroxylase causes 90% of instances of congenital adrenal hyperplasia (CAH), whereas loss of 11-b hydroxylase causes 10% of cases.

Pathway of 21-b hydroxylase deficiency

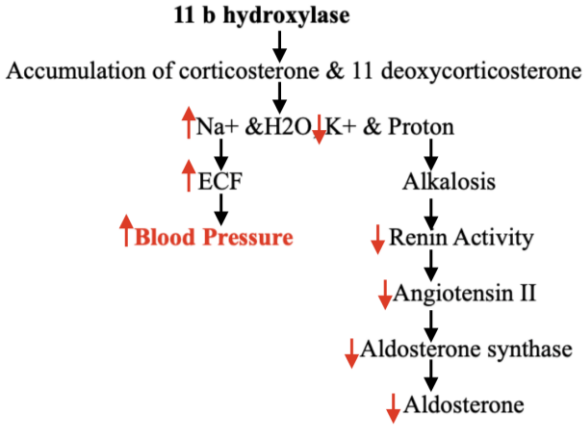
Physiological changes in 21-b hydroxylase deficiency



Pathway of 11-b hydroxylase deficiency



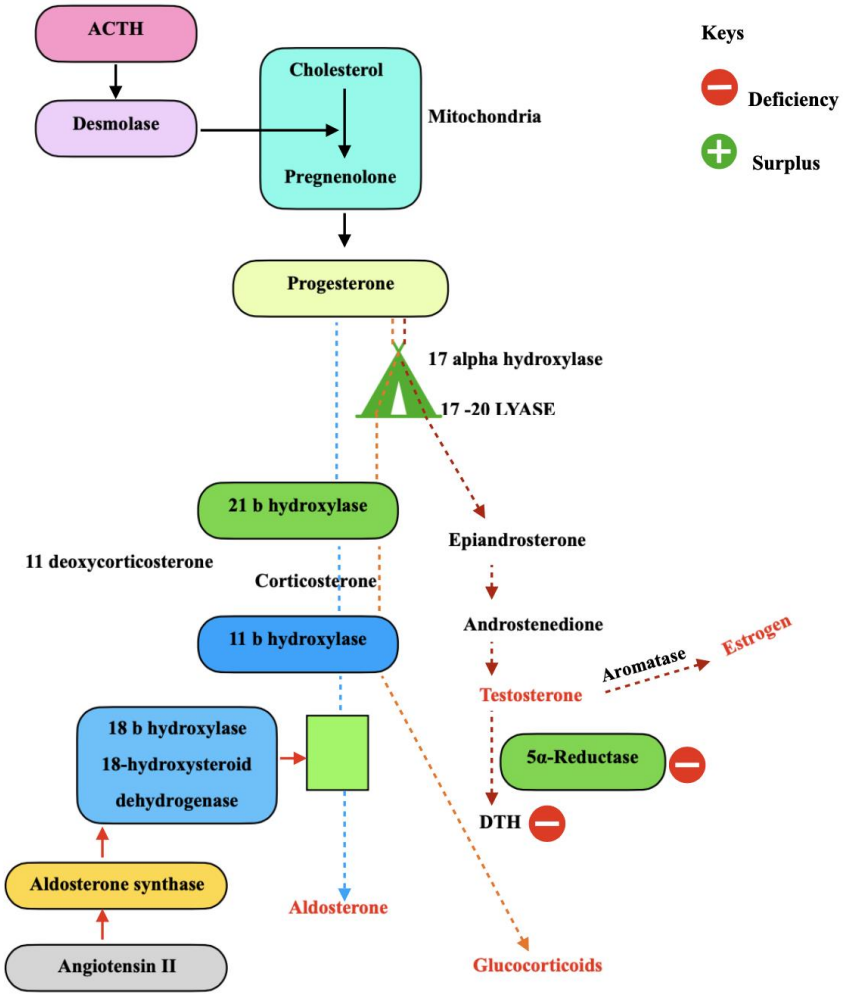
Physiological changes in 11-b hydroxylase deficiency



3. Penis at 12 syndrome

The 5-alpha reductase deficiency affects male sexual development before birth and during puberty. With one X and one Y chromosome in each cell and male gonads, individuals with this condition are genetically masculine (testes). Their bodies are not producing enough dihydrotestosterone (DHT), a hormone. In order for the exterior sex organs to grow normally before birth, DHT, a crucial hormone for male sexual development, must be present. When born, some kids with a rare genetic disorder look like girls, but around the time of puberty, they start to develop a penis and testicles.

Pathway of 5-alpha reductase deficiency



CONCLUSION

Both the chemical and biological properties of steroid hormones allow for their classification into six distinct groups in mammalian systems. Estrogens, progesterone, androgens, mineralocorticoids, glucocorticoids, and vitamin D all fall within this category. Because of their importance in so many different physiological and pathological processes, steroid hormones have been the subject of intensive study for the better part of a century. The endocrine activity of the mammalian gonads and adrenal glands metabolizes the lipid cholesterol to create the steroid repertoire, which makes up the vast bulk of the circulating steroids.

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