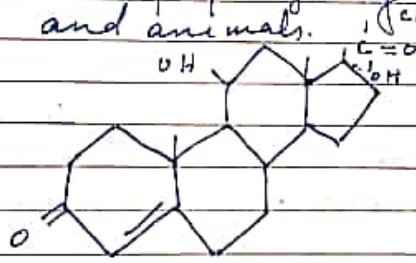
BIOSYNTHESIS OF STEROID HORMONES

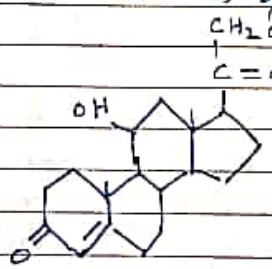
Steroid hormones → Steroid hormones are a group of hormones, derived from cholesterol from the class of compounds known as Steroids. They are secreted by the adrenal cortex, Testis and ovaries, and by the Placenta during pregnancy. on the basis of their functions, Steroid hormones have been classified into five groups

(a) Glucocorticoids (b) Mineralocorticoids (c) Androgens (d) Oestrogens and Progesterons.

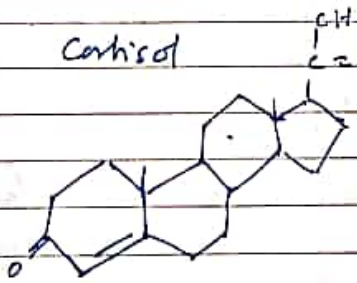
Steroids are class of natural or synthetic organic compounds characterized by a molecular structure of 17 carbon atoms arranged in four rings, Steroids are important in biology which includes all sex hormones corticol hormones, bile acids and many other physiologically active substances of plants and animals.



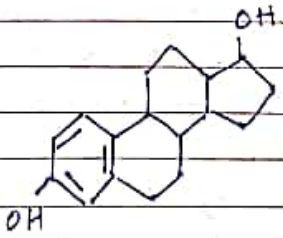
Cortisol



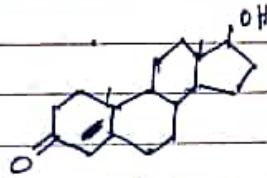
Corticosterone



Progesterone



β estradiol



Testosterone

Fig → Chemical formula's of some important Steroids.

All steroids are related to a characteristic molecular structure composed of 17 carbon atoms arranged in four rings conventionally denoted by the letters A, B, C and D bonded to 28 hydrogen atoms.

STEROID BIOSYNTHESIS – Steroidogenic enzymes are responsible for the biosynthesis from cholesterol of various steroid hormones including glucocorticoids, mineralocorticoids, Progestins androgens and estrogens. They consist of several specific cytochrome P_{450} enzymes (CYP), hydroxysteroid dehydrogenases (HSDs) and steroid reductases (Miller 1988) Numerous organs are known to have the capacity to synthesize biologically active steroids, including the adrenal gland, testis, ovary, brain placenta and adipose tissue. Three endocrine organs which mainly produces the steroids hormones are described below –

Synthesis of all steroid hormones starts with the conversion of cholesterol to pregnenolone by CyP11A (cholesterol side chain cleavage) CYP11A is bound to inner membrane of the mitochondrion and is found in steroidogenic tissues, Pregnenolone is converted to progesterone by 3β hydroxysteroid dehydrogenase (3β HSD) one of several non CYP_{450} enzymes involved in steroidogenesis found in both mitochondria and smooth endoplasmic reticulum 3β-HSD is widely distributed in steroidogenic and non steroidogenic tissues and consists of two isoenzymes in steroidogenic tissues such as adrenal testis, and ovary. whereas type I is found in placenta and in non steroidogenic tissues such as liver, kidney and skin Pregnenolone and Progesterone form the precursors for all other steroid hormones

STEROIDOGENESIS IN THE ADRENAL CORTEX—

The Adrenal gland is the most important steroid producing organ of human body essential for survival (Addison 1855). All steroidogenic process takes place in Adrenal cortex which is divided into three zones

1. Outer Zona glomerulosa
2. Middle zona fasciculata
3. Inner zona reticularis. (Neville and O'Hare)

Each zone is responsible for synthesis of a specific set of steroid hormones, the mineralocorticoids, glucocorticoids and weak androgens respectively (Miller and Pyrell, 1995)

Steroid production is regulated by specific external stimuli, such as adreno corticotropic hormone (ACTH) which mainly induces production of glucocorticoid and weak androgen production via the CAMP mediated Protein Kinase A (PKA) Pathway (Rainey, 1999) that activates factors such as steroidogenic acute regulatory protein and steroidogenic factor 1 (SF1), angiotensin II and Potassium, which increase mineralocorticoid synthesis via the inositol triphosphate / diacylglycerol mediated protein Kinase C (PKC) Pathway

Mineralocorticoids are essential for survival as they tightly regulate the Na^+/K^+ Balance in extracellular fluids, Glucocorticoids are important in glucose homeostasis and response of the organism to stressors and are important for fetal lung development, immune modulation and maintenance of normal function of a variety of tissues.

Steroid 21 hydroxylase (CYP21) is an essential enzyme for the biosynthesis of minerals and glucocorticoids. It is expressed in the SER of the all three zones and is responsible

for the conversion of Progesterone and 17α hydroxy progesterone to 11-deoxycorticosterone (Mineralo corticoid pathway) and 11-deoxycortisol (glucocorticoid pathway) respectively. These precursors are converted to the biologically active hormones aldosterone and cortisol by aldosterone synthetase (CYP11B2) and steroid 11β hydroxylase (CYP11B1) respectively. ~~These precursors are in turn converted into biologically active hormones, aldosterone and cortisol by~~ These two mitochondrial enzymes are unique to adrenal cortex.

The adrenal weak androgens are formed by CYP17 a single enzyme with both 17α hydroxylase and 17,20 lyases activity.

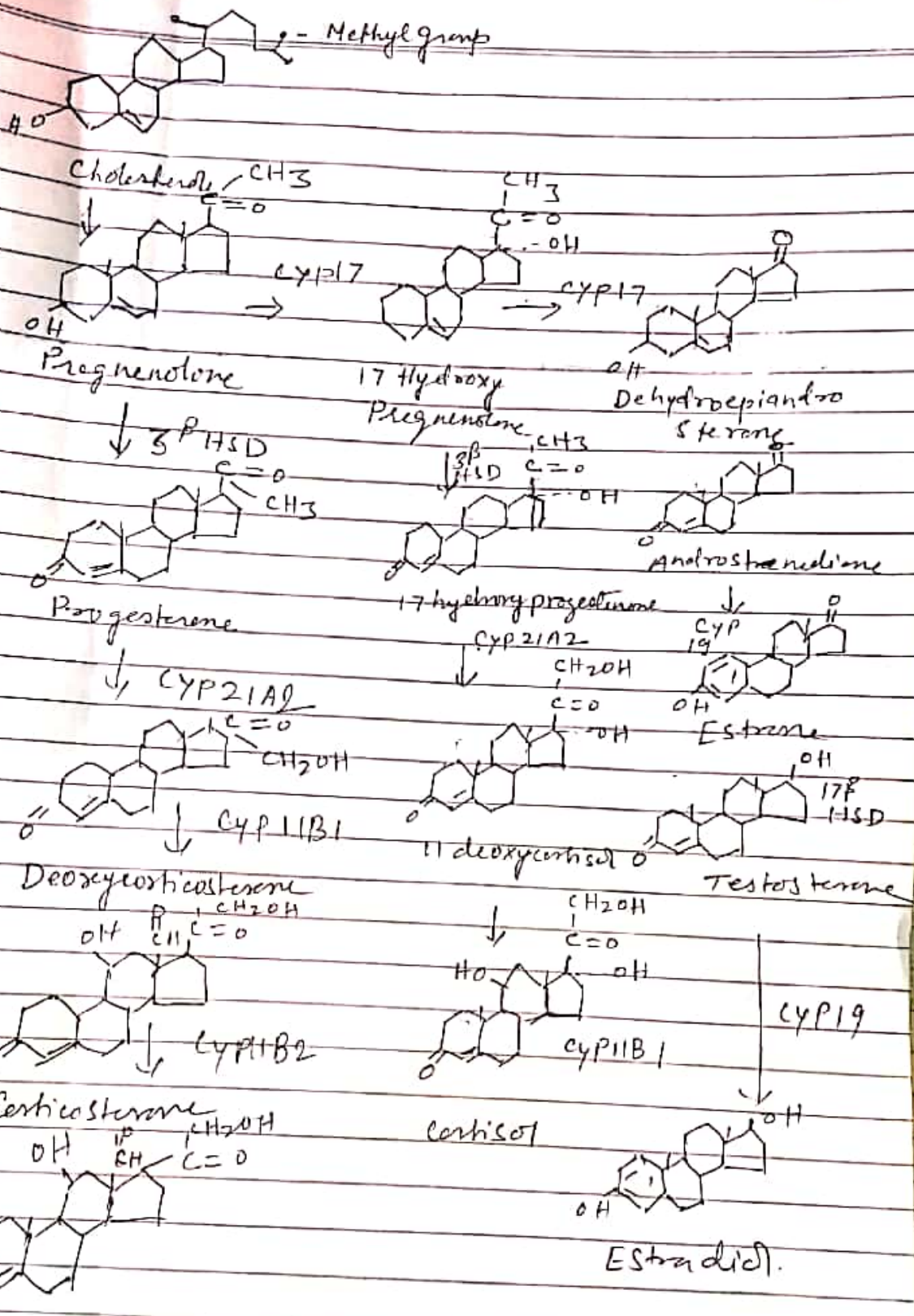
STEROIDOGENESIS IN TESTIS → The function of Testis is to produce fertile sperm for procreation and steroid hormones for sexual and reproductive function. Follicle Stimulating hormone (FSH) stimulates male germ cells to develop into mature sperm, by the process of Spermatogenesis. These stem cells are continuously renewed by mitosis for most of the lifetime of human males, FSH binds to FSH receptors on sertoli cells and stimulates the cAMP mediated second messenger Pathway, to stimulate the production of testosterone from Cholesterol.

Leutinizing hormone induces the various cytochrome P450 enzymes and dehydrogenases involved in testosterone synthesis in Leydig cells. including CYP17, 17,20-lyase the key activity directing the biosynthesis of steroids towards the sex hormones.

Leydig, Sertoli and germ cells further express low levels of aromatase which converts testosterone into estradiol for spermatogenesis and mitosis in spermatogonia

STEROIDOGENESIS IN OVARIES - The main role of ovary is to produce eggs for fertilization and steroid hormones for sexual and reproductive function. The ovum inside the developing follicle is directly surrounded by layers of granulosa cells followed by theca cells which is where steroidogenesis take place. The theca interna is highly vascularized and produces large amounts of Progesterone and androgens which acts as a precursor for estrogen synthesis in the granulosa cells.

Androstenedione and testosterone diffuse into the neighboring poorly vascularized granulosa cells where they are converted to predominantly estradiol via the action of aromatase and 17β-HSD type 1 and 7 which leads to conversion of estrone to estradiol. In the preovulatory follicular stage, during which the follicle matures, estrogen synthesis increases gradually due to up regulation of aromatase by LH and FSH. After the LH surge, the follicle enters the luteal phase and becomes a corpus luteum, which synthesized progesterone. Decreased LH concentration and decreased aromatase expression results in declining estrogen production while a concurrent increase in CYP11A and 3β-HSD activity promotes the synthesis of progesterone via its receptor initiates the process of follicle rupture.



Biosynthetic Pathways for major classes of Steroid hormones.

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