

**SCHOOL OF MEDICINE AND HEALTH SCIENCES
DIVISION OF BASIC MEDICAL SCIENCES
DISCIPLINE OF BIOCHEMISTRY & MOLECULAR BIOLOGY**

PBL SEMINAR: SEX HORMONES PART 1 – An Overview

What are steroid hormones?

- ❑ Steroid hormones are the group of hormones that are synthesized from Cholesterol.
- ❑ Important mammalian steroid hormones along with the structure of the precursor, Pregnenolone are show in **Fig. 1**.

Briefly outline the pathways for biosynthesis of steroid hormones:

- ❑ Pathways for the biosynthesis of steroid hormones are shown in **Fig. 2**.
- ❑ Particular steroid hormone class synthesized by a given cell type depends upon:
 - Its complement of peptide hormone receptors,
 - Its response to peptide hormone stimulation and
 - Its genetically expressed complement of enzymes.

How do steroid hormones exist in plasma?

- ❑ Steroid hormones are not soluble in aqueous medium, thus they bind to specific hormone binding Glycoproteins in plasma (bound fraction of hormone).
- ❑ A small amount of the steroid hormone usually remains unbound or free in plasma.
- ❑ Unbound or “Free’ fraction of the hormone in plasma is biologically active.
- ❑ Measurement of Free hormone status or binding protein levels is important in the diagnosis of patients with steroid hormone disorders.

What is the general mode or mechanism of action of steroid hormones?

- ❑ Steroid hormones exert their action by passing through the cell membrane and binding to intracellular receptors (formation of steroid hormone-receptor complex)
- ❑ Steroid Hormone-Receptor Complex exerts its action in the Nucleus of Target cells.
- ❑ Steroid Hormone-Receptor Complex binds to Specific Nucleotide Sequences in the DNA of Responsive Genes.
- ❑ These DNA sequences are identified as Hormone Responsive Elements (HREs).
- ❑ Interaction of steroid hormone-receptor complexes with DNA leads to altered rates of Transcription of the associated Genes in Target cells.

What are the Sex Steroid Hormones?

- ❑ Both Testosterone and Estradiol are known as Sex Steroid Hormones.
- ❑ Testosterone: Testes synthesize the Principal Androgen in male.
- ❑ Estradiol (Oestradiol): Principal female hormone is secreted by the Ovaries, varies widely in concentration in plasma throughout the female menstrual cycle.
- ❑ Steroids with Estradiol-like action are called Estrogens.
- ❑ **Progesterone** is a product of the Ovary and is secreted when a Corpus Luteum forms after Ovulation.
- ❑ Normal female plasma contains Testosterone:
 - Half comes from the Ovary and
 - Half from peripheral conversion of **Androstenedione** and **Dehydroepiandrosterone (DHEA) Sulphate**, secreted by the Adrenal Cortex.
- ❑ Estradiol is present in low concentration in normal male plasma.

What is the function of SHBG and how does it affect plasma levels of the Sex Steroids?

- ❑ Testosterone and Estradiol circulate in plasma mostly bound to plasma proteins, particularly Sex Hormone Binding Globulin (SHBG).
- ❑ SHBG has a higher affinity for Testosterone than for Estradiol.
- ❑ Estradiol stimulates SHBG synthesis by the liver,
- ❑ Testosterone decreases SHBG synthesis by the liver
- ❑ Plasma concentration of SHBG in females is twice that in males.
- ❑ Factors, which alter the concentrations of SHBG in plasma, alter the Ratio of Unbound Testosterone to Unbound Estradiol.
- ❑ In both sexes the effect of:
 - An increase in SHBG is to increase Estradiol-like effects, (**Why?**)
 - A decrease in SHBG is to increase Androgen effects (**Why?**)
- ❑ As Estradiol it increases SHBG concentration and Testosterone decreases it, this system functions as a Biological Servomechanism.
- ❑ Testosterone and SHBG concentrations are sometimes reported by the laboratory as a Ratio (the Free Androgen Index), which gives a clearer indication of Androgen status than does serum Testosterone alone.

What axis regulates the secretion of the sex steroids?

- ❑ Secretion is regulated by the Hypothalamic-Pituitary-Gonadal Axis (HPG-axis)
- ❑ Hypothalamus releases the Hormone called Gonadotropin-Releasing Hormone (GnRH)
- ❑ GnRH acts on the Anterior Pituitary to stimulate synthesis and release of the Gonadotropins:
 - Luteinizing Hormone (LH) and
 - Follicle-Stimulating Hormone (FSH).
- ❑ Gonadotropins (LH and FSH) act cooperatively on the Ovaries in the female and the Testes in the male to stimulate Sex Hormone secretion and reproductive processes
- ❑ Regulation of the secretion of sex steroid hormones is by Negative Feed-back on HPG-axis.
- ❑ Inhibin produced by the Gonads also feed back inhibits the production of FSH.

What is Congenital Adrenal Hyperplasia (CAH) and what causes it?

- ❑ Congenital Adrenal Hyperplasia (CAH) is a group of metabolic disorders characterized by deficiencies of activity of Adrenal Enzymes needed to make Adrenal Steroids.
- ❑ Adrenal Gland produces 3 groups of Steroid Hormones, based on their Physiologic function:
 - ❑ Glucocorticoids (Primarily Cortisol), which serve numerous roles in the regulation of metabolism, and are anti-inflammatory.
 - ❑ Mineralocorticoids (Primarily Aldosterone), which activate the Na^+/K^+ and Na^+/H^+ exchanges in the distal renal tubule.
 - ❑ Androgens.

- The deficiency in activity of the Adrenal enzyme results in the following:
 - Inadequate production of Adrenal Glucocorticoids,
 - Inadequate production of Mineralocorticoids,
 - Excessive production of Adrenal Androgens.

- Deficiency of the enzyme 21-Hydroxylase in the Steroid biosynthetic pathway is the most common form of CAH.
- CAH is an autosomal recessive disorder.
- Deficiency of 21-Hydroxylase prevents the normal biosynthesis of Cortisol and Aldosterone, both of which have a 21-Hydroxylated Carbon atom.
- Deficiency of 21-Hydroxylase causes large amounts of Steroids to be shunted to the pathways that lead to production of the Adrenal Androgens:
 - Androstenedione and
 - Dehydroepiandrosterone (DHEA)

- Synthesis of these steroids does not require the 21-Hydroxylase enzyme
- Anterior Pituitary and Hypothalamus sense the low level of Cortisol, this leads to the production of high levels of Corticotrophin (ACTH) in an attempt to stimulate the Adrenal glands.
- It is the elevated levels of Corticotrophin (ACTH) that:
 - Cause the Adrenal Glands to become Hyperplastic and
 - Stimulate the production of large amounts of early steroids that flow into the normally minor pathways of Androgen synthesis.

What are the different forms of 21-Hydroxylase deficiencies?

There are two major forms of 21-Hydroxylase deficiencies.

- “Classic” form of CAH results from complete or a near complete block of enzyme activity and is clinically present at birth.
 - “Non-classic” (late onset) form of CAH involves only partial blockade of enzymatic activity. It is usually diagnosed later in life, and is symptomatically milder than the classic form
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- Aldosterone synthesis is impaired in all patients with “Classic” 21-Hydroxylase deficiency
 - Two variants of the “Classic” form exist that are distinguished by the severity of the 21-Hydroxylase defects.
 - The two variants are:
 - Salt-Losing variant: Aldosterone synthesis is insufficient to prevent Adrenal crisis because of salt loss.
 - “Simple Virilizing” variant (i.e., classic CAH without salt wasting): there is sufficient, but diminished Aldosterone production in response to Sodium depletion.
 - Note that the distinction between these two variants of Classic disease on a molecular basis is not absolute and they represent a continuous spectrum of disease severity.

How are these variants expressed in affected neonates/infants?

Effect on Female:

- Girls with the Classic Simple Virilizing or Salt-Losing forms of 21-Hydroxylase deficiencies are born with **Genital Ambiguity** ranging from mild Clitoromegaly to a fully Masculinized Penile Urethra.
- At birth masculinized female infants may be incorrectly classified as boys.
- This error is usually recognized when a Salt-Losing Crisis develops (at 1 to 4 weeks of age).

Effect on Male:

- Boys with the Salt-Losing form appear normal at birth and are therefore at high risk for a Salt-Losing Adrenal Crisis because there is no obvious Phenotypic Clue to the underlying Adrenal defect.
- The inability to retain Sodium and excrete Potassium from the Renal Tubules results in:
 - Dehydration, Failure to thrive, Vomiting,
 - Hypoglycemia, Hyponatremia, Hyperkalemia,
 - Acidosis and can lead to Cardiovascular Collapse.
- In boys with the non-salt-losing form, diagnosis is often delayed until virilization is apparent.

How is the Non-classic form presented?

- A milder, “Non-classic” form of CAH (also called “Late Onset” or “Acquired”) does not produce Ambiguous Genitalia in female infants.
- It presents with symptoms of mild virilization in older children or women.
- The clinical features resulting from Androgen excess can occur at any age and consist of:
 - Premature Puberty, Cystic Acne, Short Adult Stature, Menstrual Irregularities, Secondary Amenorrhea, Hirsutism or Infertility.

What endocrine systems are affected by the 21-Hydroxylase defects?

The 21-Hydroxylase defects disrupt three distinct Endocrine Systems:

- HPA axis, which regulates Cortisol production;
- RAA axis, which regulates Aldosterone production; and
- HPG axis, which regulates Sex Steroid production.

Briefly explain the effect of 21-hydroxylase defects on the three enzyme systems

- Deficient Cortisol production activates the HPA axis to produce increased amounts of Corticotropin Releasing Hormone (CRH) and ACTH, which lead to Adrenal Hyperplasia and increased overproduction of Androgens.
- Deficient Aldosterone production leads to Salt Loss and activates the RAA axis.
- Increase in Adrenal Androgens affects the HPG axis in two ways:
 - i. In the short term it suppresses the axis through the Negative Feed-back effects of Sex Steroids;
 - ii. In the long term it activates the axis by advancing Somatic and Skeletal maturation with resultant secondary central Precocious Puberty.

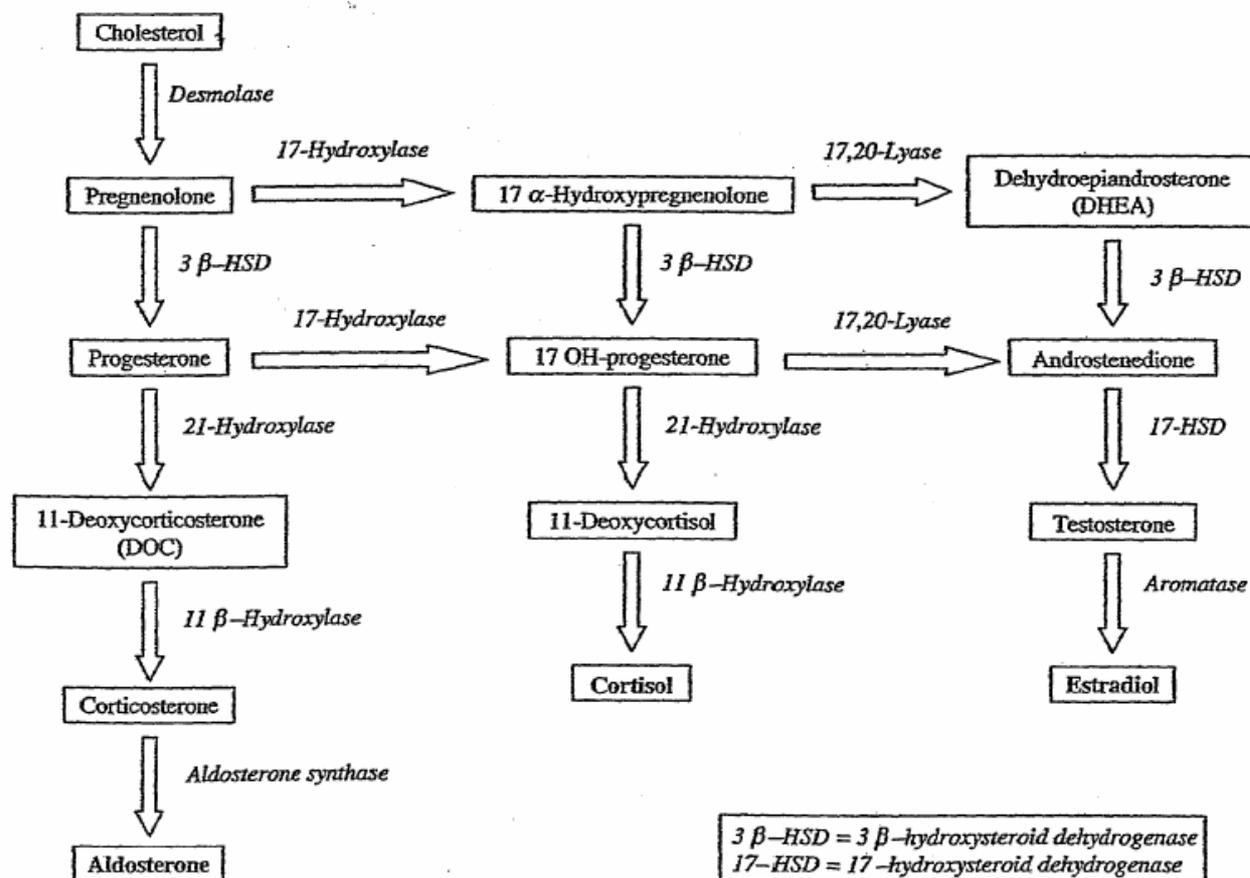
TAKE NOTE:

- Interaction between the RAA and HPA axis is of immense clinical importance for the management of patients with CAH.
- Both ACTH and Cortisol play a role in the Homeostatic regulation of Intravascular Volume.
- Salt Loss resulting from a defect in Aldosterone production activates not only the RAA axis but also the HPA axis.
- Failure to suppress ACTH-mediated 17-Hydroxy-progesteron (17-OPH) and Progesterone secretion with Glucocorticoid further increases salt loss because of the ability of these steroids to compete with Aldosterone for the Renal Tubular Mineralocorticoid Receptor.
- Optimal control of ACTH secretion in 21-Hydroxylase deficiency requires replacement of both Mineralocorticoid and Glucocorticoid.
- Neglecting either of these dual influences on ACTH secretion leads to Hyper-secretion of both ACTH and Adrenal Androgens.
- At birth, the Ambiguous Genitalia of the affected female infant should raise a clinical suspicion of CAH.
- On biochemical testing these patients may have elevated 17-Hydroxyprogesterone values and elevated Adrenal Androgen levels.

How is CAH diagnosed?

- Diagnosis of CAH is by measurement of plasma 17-Hydroxyprogesterone (17-OHP).
- Levels of this steroid (which is “behind” the metabolic block in 21-Hydroxylase deficiency) are markedly elevated in untreated patients.
- Untreated patients have:
 - Elevations of Adrenal Androgens, and
 - If salt wasting is present, the typical Electrolyte profile (Hyponatremia and Hyperkalemia) of Adrenal Insufficiency is present.
- Salt wasting patients also have elevated plasma Renin activity.
- Infants with severe virilization failure (Proximal Hypospadias and Non-palpable Testes) should be evaluated for Congenital Adrenal Hyperplasia by obtaining a Karyotype and measuring 17-Hydroxyprogesterone.
- Females with Congenital Adrenal Hyperplasia have a normal Female Karyotype (46 XX).
- Such females are potentially fertile.
- By replacing Cortisone, the overproduction of Androgenic Hormones can be decreased.
- Correction of the metabolic abnormalities is accomplished:
 - By providing the missing Glucocorticoid, and Mineralocorticoid, and,
 - In the patient with Acute Salt-Wasting Crisis, correcting the Fluid and Electrolyte disturbances.
- Long-term management involves:
 - Replacement steroids,
 - Monitoring:
 - Growth (as a marker of sufficiency of suppression of Adrenal Androgen production),
 - Electrolytes, 17-OHP, D4-Androstene-dione, and plasma Renin activity (as markers of sufficiency of mineralocorticoid activity).

Figure 2:
Diagram the steroid hormone pathway.



Steroid Pathway.