SEX STERIOD HORMONES – I: An Overview

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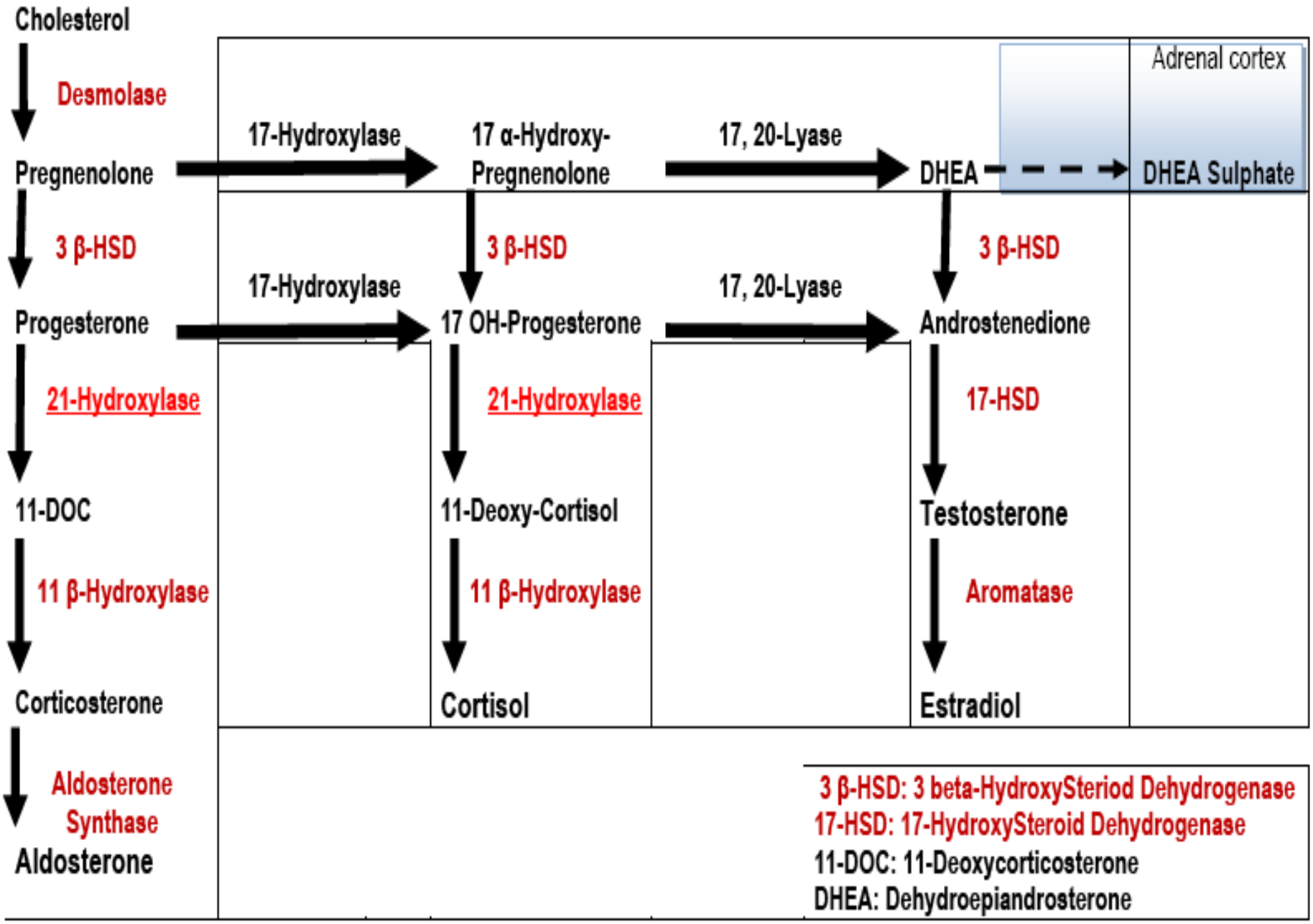
What are the Steroid hormones?

- **Hormones synthesized from Cholesterol**;
- Some important steroid hormones:
  - **Progesterone**: secreted in Corpus Luteum, involved in Luteral phase of menstrual cycle, differentiation of mammary glands;
  - **Estradiol (Oestradiol)**: Estrogen, produced in ovary, responsible for secondary female sex characteristics;
  - **Testosterone**: Androgen, produced in testes, responsible for secondary male sex characteristics;
  - **Aldosterone**: Principal Mineralocorticoid from Adrenal Cortex;
  - **Cortisol**: Principal Glucocorticoid from Adrenal Cortex;

Outline the pathways for biosynthesis of steroid hormones

- Pathways for biosynthesis of steroid hormones usually presented as a flow chart;
- Specific steroid hormone synthesized depends on:
  - Complement of Peptide Hormone Receptors in tissue,
  - Tissue response to Peptide Hormone Stimulation,
  - Genetically Expressed Complement of Enzymes in cells
- Flow chart does not go to completion in all tissues;
- **Fig. 1**: Schematic diagram of pathways for biosynthesis of different steroid hormones;

Fig. 1: Flow diagram of pathways for biosynthesis of steroid hormones



How do steroid hormones exist in blood plasma?

- Steroid hormones are **Hydrophobic**,
  - Exist in plasma mainly bound to Specific Hormone Binding Glycoproteins (Bound Fraction);
- Small amount of Steroid hormone exist Freely in plasma (Unbound or Free Fraction);
- **Unbound or "Free" fractions of steroid hormones in blood plasma are the biologically active fractions,**
- Measurements of "Free Fractions" of steroid hormones or Binding Protein levels are important for diagnosis of patients with certain steroid hormone disorders;

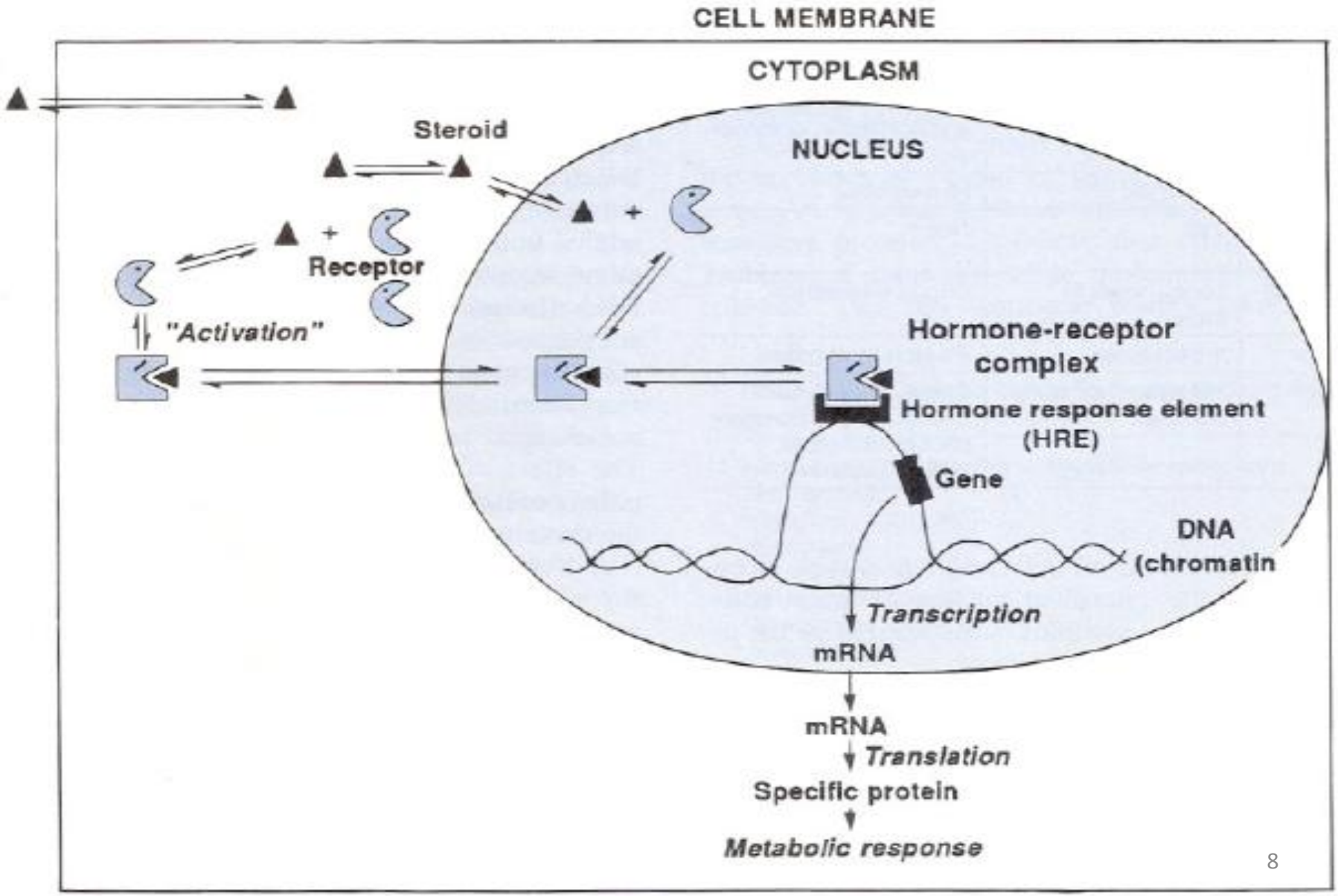
What is the general mode of action of steroid hormones?

- Free Fractions of Steroid hormones can pass through cell membrane in target tissues and bind to Intracellular receptors, forming **Steroid Hormone-Receptor Complex**,
- The Complex exerts its action on Nucleus of Target cells,
- Steroid Hormone-Receptor Complex binds to Specific Nucleotide Sequences on DNA of Responsive Genes,
  - Specific Nucleotide Sequences in DNA are called **Hormone Response Elements (HRE)**,
- Interaction of steroid hormone-receptor complexes with HRE in DNA leads to altered rates of Transcription of associated Genes in Target cells;

- Resulting in Transcription of the gene, to form Messenger RNA (m-RNA),
- Messenger RNA is released in Cytoplasm, interacts with Ribosome for Translation to occur,
- Translation leads to formation of Polypeptide chain,
- Polypeptide chain undergoes Post-translational modification in Golgi apparatus to form functional peptide or protein; **(Fig. 2)**

Fig 2: Schematic diagram, mode of action of steroid hormones

(Harper's Biochem, 24th Ed , 1996)



How does SHBG affect plasma levels of Sex Steroid Hormones?

- Testosterone and Estradiol circulate in blood plasma mostly bound to **Sex Hormone Binding Globulin (SHBG)**;
- SHBG has **higher affinity** for Testosterone than Estradiol,
- **Testosterone inhibits SHBG** synthesis in the liver,
- **Estradiol stimulates SHBG synthesis in** the liver,
- SHBG levels in females is about twice that in males,
- Factors that alter the concentrations of SHBG in blood plasma alter the Ratio of Free Testosterone to Free Estradiol,

- In both sexes the effect of:
  - An increase in SHBG level in blood plasma is to increase Estradiol-like effects, (**Why?**)
  - A decrease in SHBG level in blood plasma is to increase Androgen effects (**Why?)**

- As Estradiol itself increases SHBG level in blood plasma and Testosterone decreases it, the system functions as a Biological Servomechanism;

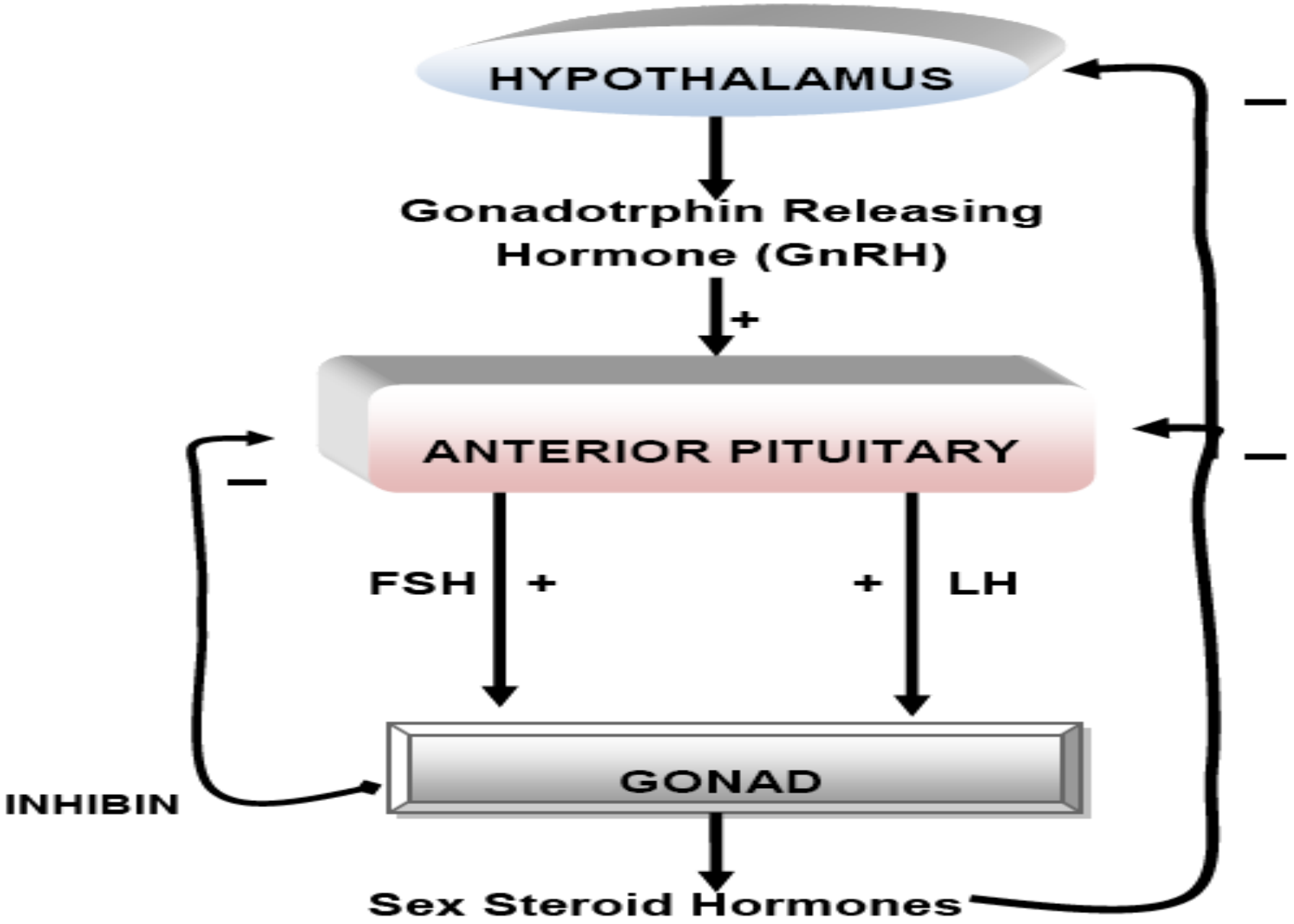
- Testosterone and SHBG concentrations in plasma are sometimes reported by laboratory as a Ratio **Free Androgen Index (FAI)**, which gives a clearer indication of Androgen status than does plasma Testosterone alone;

$$\text{FAI} = \frac{[\text{Total Testosterone}]}{[\text{SHBG}]}$$

What axis regulates secretion of sex steroid hormones?

- Regulation of secretion of sex steroids is by Negative Feedback mechanism on **HPG –Axis (Fig 3)**
  - **HPG-Axis:** Hypothalamic-Pituitary-Gonadal Axis;
- Hypothalamus releases **Gonadotrophin-Releasing Hormone (GnRH)**, which acts on Anterior Pituitary to produce **Gonadotrophins**:
  - **Luteinizing Hormone (LH),**
  - **Follicle-Stimulating Hormone (FSH)**
- Gonadotrophins act on Ovaries in females or Testes in males to stimulate Sex Hormone secretion,
- **Inhibin** from Gonads feedback inhibits FSH secretion;
- Sex steroid feedback inhibit LH secretion;

Fig. 3: Hypothalamus –Pituitary-Gonad Axis,
Negative Feedback regulation of secretion of Sex steroids



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

- Congenital Adrenal Hyperplasia (CAH):
  - Group of metabolic disorders characterized by lack of Adrenal Enzymes for biosynthesis of Adrenal Steroids;
- Adrenal Gland produces 3 groups of Steroid Hormones, based on their Physiologic function:
  - Glucocorticoids (Primarily Cortisol), involved in the regulation of metabolism, and are anti-inflammatory;
  - Mineralocorticoids (Primarily Aldosterone), involved in regulation of Na^+/K^+ and Na^+/H^+ exchanges in distal renal tubule;
  - Androgens, involved in regulation of secondary male characterises;

- Deficiency in Adrenal enzyme results in:
  - Inadequate production of Adrenal Glucocorticoids,
  - Inadequate production of Mineralocorticoids,
  - Excessive production of Adrenal Androgens;
- Deficiency of **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 biosynthesis of
  - **Cortisol,**
  - **Aldosterone,** **WHY???**
- Because both have **21-Hydroxylated Carbon atom;**

- Deficiency of 21-Hydroxylase causes large amounts of Steroids to be shunted to the pathways that lead to production of **Adrenal Androgens**:
  - **Androstenedione,**
  - **Dehydroepiandrosterone (DHEA);**
- These steroids does not require 21-Hydroxylase enzyme,
- Resultant low level of Cortisol is detected by Anterior Pituitary and Hypothalamus,
- It leads to increased production of Adrenocorticotropic hormone (ACTH) in an attempt to stimulate the Adrenal glands;

- Elevated levels of ACTH causes:
  - Adrenal Glands to become Hyperplasic, and
  - Stimulate production of large amounts of early steroids that flow into the normally minor pathways of Androgen synthesis;
- Leads to increased production of Androgens;

What are the different forms of 21-Hydroxylase deficiencies?

- 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 partial blockade of enzymatic activity;
    - It is usually diagnosed later in life, symptomatically milder than the Classic form;
- **Aldosterone** synthesis is impaired in all patients with "Classic" 21-Hydroxylase deficiency;

- **Two variants** of “Classic” form that are distinguished by the severity of 21-Hydroxylase defects;
  - **Salt-Losing variant**:
    - Aldosterone synthesis is insufficient to prevent Adrenal crisis because of salt loss;
  - “**Simple Virilizing**” variant (Classic CAH without salt wasting):
    - There is sufficient, but diminished Aldosterone production in response to Sodium depletion;
- **NB**: Distinction between these two variants of Classic disease on a molecular basis is not absolute and they represent a continuos spectrum of disease severity;

How are these variants expressed in affected neonates infants?

- Effect on Females:
  - Girls with Classic Simple Virilizing or Salt-Losing forms of 21-Hydroxylase deficiencies are born with **Genital Ambiguity** ranging from mild Clitoromegaly to fully Masculinised Penile Urethra
  - At birth masculinised 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 Salt-Losing form appear normal at birth and are therefore at high risk for Salt-Losing Adrenal Crisis because there is no obvious Phenotypic Clue to the underlying Adrenal defect;
  - Inability to retain Sodium and excrete Potassium from Renal Tubules results in:
    - Dehydration, Hyponatraemia, Hyperkalemia,
    - Hypoglycaemia, Vomiting,
    - Acidosis that can lead to Cardiovascular Collapse,
    - Failure to thrive,
- In boys with non-salt-losing form, diagnosis is often delayed until virilisation is apparent;

How is the Non-classic form presented?

- A milder, “Non-classic” form of CAH (“Late Onset” or “Acquired”) does not produce Ambiguous Genitalia in female infants;
- It presents with symptoms of mild virilisation in older children or women;
- 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 21-Hydroxylase defects?

- 21-Hydroxylase defects disrupt **Three** distinct Endocrine Systems:
  - **HPA axis** that regulates Cortisol production;
  - **RAA axis** that regulates Aldosterone production;
  - **HPG axis** that regulates Sex Steroid production;

What are the effects of 21-hydroxylase defects on the 3 Axis?

- Deficient Cortisol production activates HPA axis to produce increased amounts of CRH and ACTH, which lead to Adrenal Hyperplasia and overproduction of Androgens
- Deficient Aldosterone production leads to Salt Loss and activates the RAA axis;
- Increase in Adrenal Androgens affects HPG axis in 2 ways:
  - In **Short term** it suppresses the axis through Negative Feed-back effects of Sex Steroids;
  - In the **Long term** it activates the axis by advancing Somatic and Skeletal maturation with resultant Secondary Central Precocious Puberty;

IMPORTANT TO NOTE

- Interaction between RAA and HPA axis is of immense clinical importance for management of patients with CAH
- ACTH and Cortisol play a role in Homeostatic regulation of Intravascular Volume;
- Salt Loss resulting from defect in Aldosterone production activates the RAA axis and also 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 Renal Tubular Mineralocorticoid Receptor;

- Optimal control of ACTH secretion in 21-Hydroxylase deficiency requires replacement of Mineralocorticoid and Glucocorticoid;
- Neglecting either of these dual influences on ACTH secretion leads to Hyper-secretion of both ACTH and Adrenal Androgens;
- At birth, Ambiguous Genitalia of affected female infant should raise a clinical suspicion of CAH;
  - Laboratory tests for these patients may show:
    - **Elevated levels of 17-Hydroxyprogesterone,**
    - **Elevated levels of Adrenal Androgen;**

What are the laboratory tests for diagnosis of CAH?

- Diagnosis of CAH is by measurement of plasma level of 17-Hydroxyprogesterone (17-OHP);
- Levels of this steroid (substrate for 21-Hydroxylase) are markedly elevated in untreated patients;
- Untreated patients may also have:
  - Elevated Adrenal Androgens,
  - If Salt Wasting is present, the typical Electrolyte profile (Hyponatraemia and Hyperkalemia) of Adrenal Insufficiency will be present;
- Salt wasting patients may also have elevated plasma Renin activity;

- Infants with severe virilisation failure (Proximal Hypospadias and Non-palpable Testes) should be evaluated for CAH by obtaining a Karyotype and measuring 17-OHP;
- Females with CAH should have normal Female Karyotype (46 XX);
  - Such females are potentially fertile;
  - By replacing Cortisol, overproduction of Androgenic Hormones may decrease;

IMPORTANT TO NOTE

- Correction of metabolic abnormalities is accomplished:
  - By providing Glucocorticoid and Mineralocorticoid,
  - For patients with Acute Salt-Wasting Crisis, correcting Fluid and Electrolyte disturbances;
- Long-term management involves:
  - Replacement steroids,
  - Monitoring:
    - Growth, as 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);

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