

Congenital Adrenal Hyperplasia and Testicular Feminization Syndromes

Reproductive Block

Objectives

- Adrenal steroidogenesis
- Congenital adrenal hyperplasia syndrome

Types

Biochemical characteristics

Clinical manifestations

- Testicular feminization syndrome

Adrenal Glands

The adrenal glands comprise 3 separate hormone systems:

The zona glomerulosa:

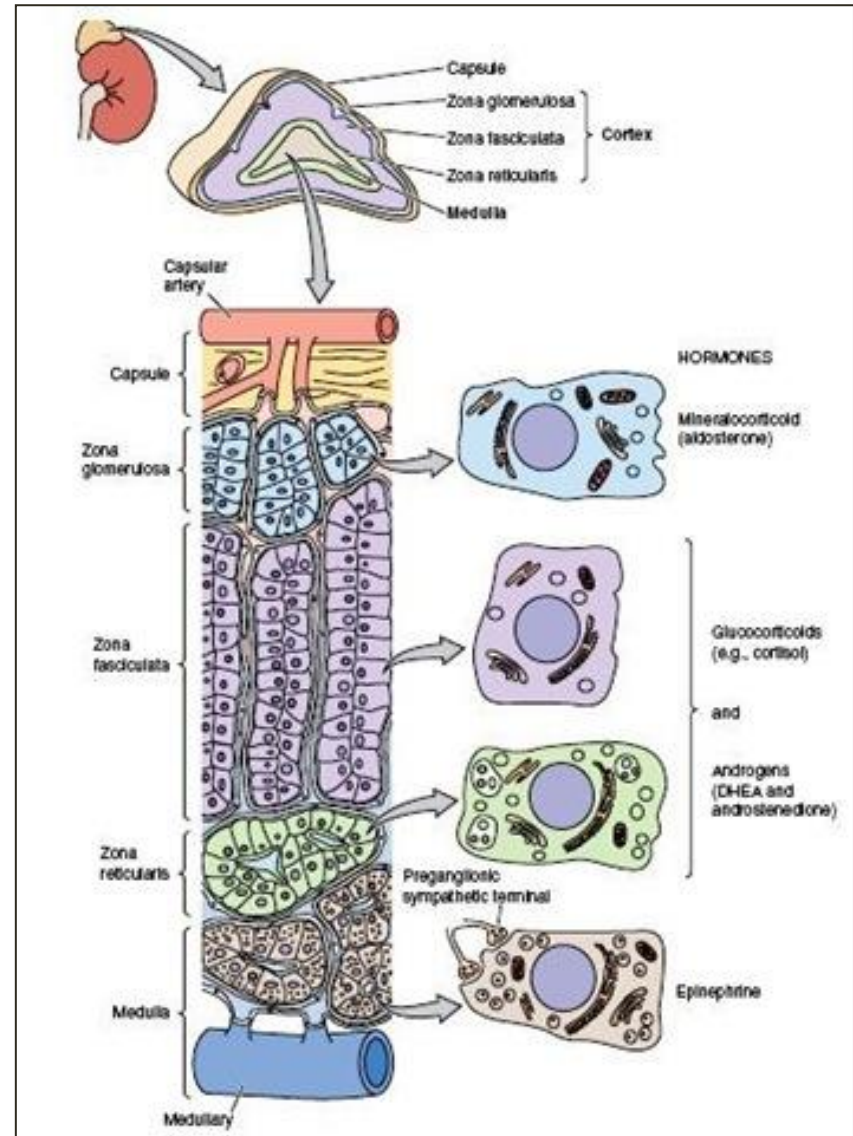
Secretes aldosterone

The zona fasciculata & reticularis:

Secrete cortisol & the adrenal androgens

The adrenal medulla:

Secretes catecholamines (mainly epinephrine)



Hermaphroditism or Intersex

- A person who has neither standard male or standard female anatomy.
Discrepancy between the type of gonads and the external genitalia
- True hermaphrodite (ovary plus testis)
- Female pseudohermaphrodite (FPH, only ovary)
- Male pseudohermaphrodite (MPH, only testis)

Glucocorticoids & Mineralocorticoids

- ***Glucocorticoids:***
 - Steroids with cortisol-like activity
 - Potent metabolic regulators & immunosuppressants
- ***Mineralocorticoids:***
 - Steroids with aldosterone-like activity
 - Promote renal sodium reabsorption

Steroidogenesis and Congenital adrenal hyperplasia syndrome

CONGENITAL ADRENAL HYPERPLASIAS (CAH)

3- β -HYDROXYSTEROID DEHYDROGENASE DEFICIENCY

- Virtually no glucocorticoids, mineralocorticoids, active androgens, or estrogens.
- Salt excretion in urine.
- Patients have female-like genitalia.
- Autosomal recessive with incidence of 1:10,000

17- α -HYDROXYLASE DEFICIENCY

- Virtually no sex hormones or cortisol are produced.
- Increased production of mineralocorticoids causes sodium and fluid retention and, therefore, hypertension.
- Patients have female-like genitalia.

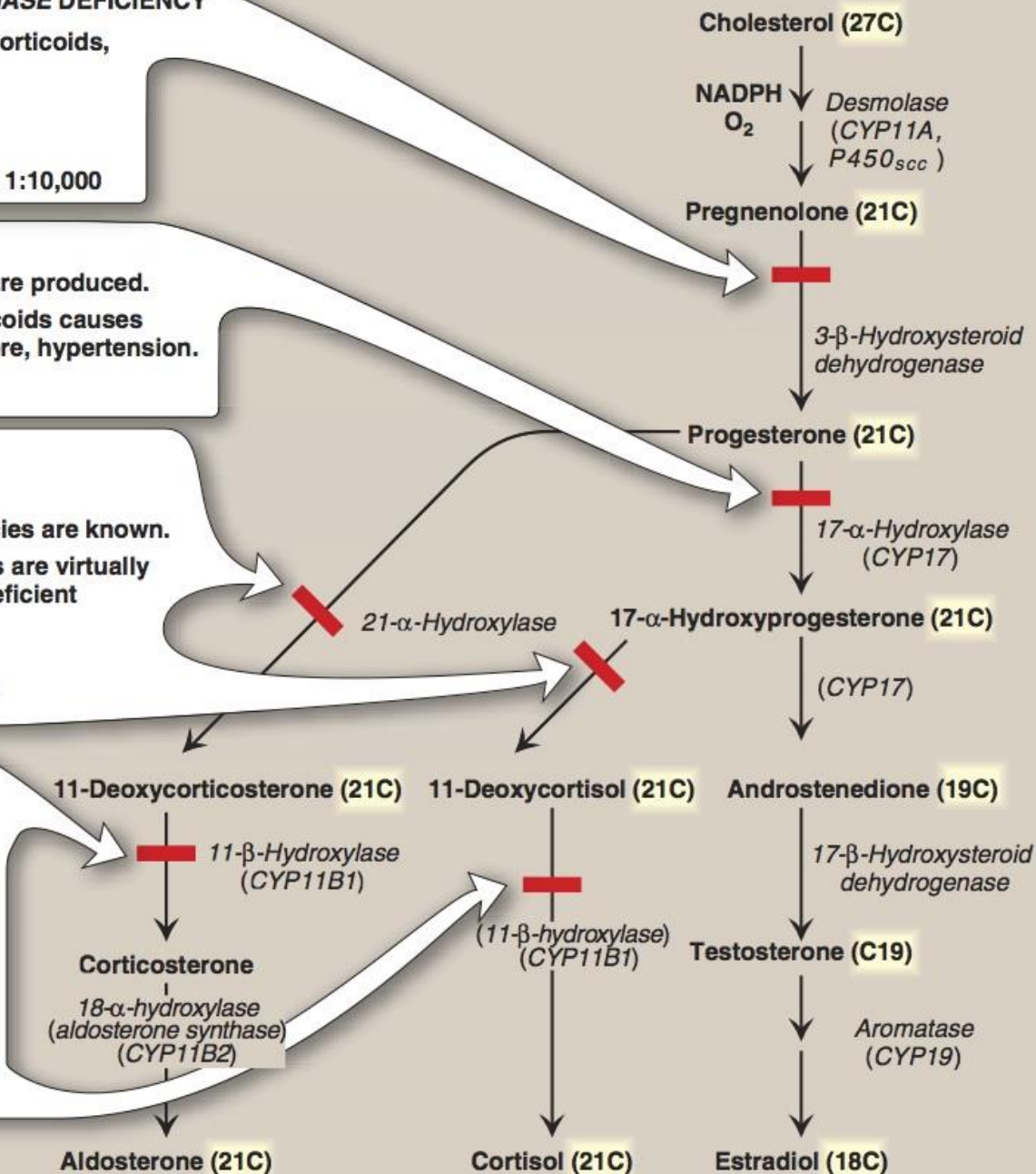
21- α -HYDROXYLASE DEFICIENCY

- Most common form of CAH (>90%)
- Partial and virtually complete deficiencies are known.
- Mineralocorticoids and glucocorticoids are virtually absent (salt wasting classic form) or deficient (non-classic form).
- Overproduction of androgens leads to masculinization of external genitalia in females and early virilization in males.

11- β 1-HYDROXYLASE DEFICIENCY

- Decrease in serum cortisol, aldosterone, and corticosterone.
- Increased production of deoxycorticosterone causes fluid retention. Because this hormone suppresses the renin/angiotensin system, it causes low-renin hypertension.
- Overproduction of androgens causes masculinization and virilization as with 21- α -hydroxylase deficiency.

STEROID HORMONE SYNTHESIS



Congenital Adrenal Hyperplasia (CAH) Syndromes

- It is the result of an inherited enzyme defect in steroid biosynthesis
- The adrenals :
 - Cannot secrete cortisol → absent negative feedback to the pituitary) → ACTH continues to drive steroid biosynthesis → adrenal hyperplasia and accumulation of cortisol precursors (depending on which enzyme is lacking)
 - Cannot secrete aldosterone → electrolyte disturbances
 - Hyponatremia
 - Hyperkalemia
- The condition might be fatal unless diagnosed early

CAH Syndromes

- 21 α -Hydroxylase deficiency
- 11 β -Hydroxylase deficiency
- 17 α -Hydroxylase deficiency
- 3 β -Hydroxysteroid dehydrogenase deficiency

21 α -Hydroxylase Deficiency

- The most common type of CAH (90%)
- Clinically:
 - Complete enzyme defect: \uparrow stimulation of adrenal androgen production \rightarrow virilization in baby girls & precocious puberty in boys.
 - Partial enzyme defect \rightarrow late onset form \rightarrow menstrual irregularity & hirsutism in young females.
- Laboratory diagnosis: \uparrow plasma [17- α -hydroxyprogesterone] as early as 4 days after birth

21 α -Hydroxylase Deficiency

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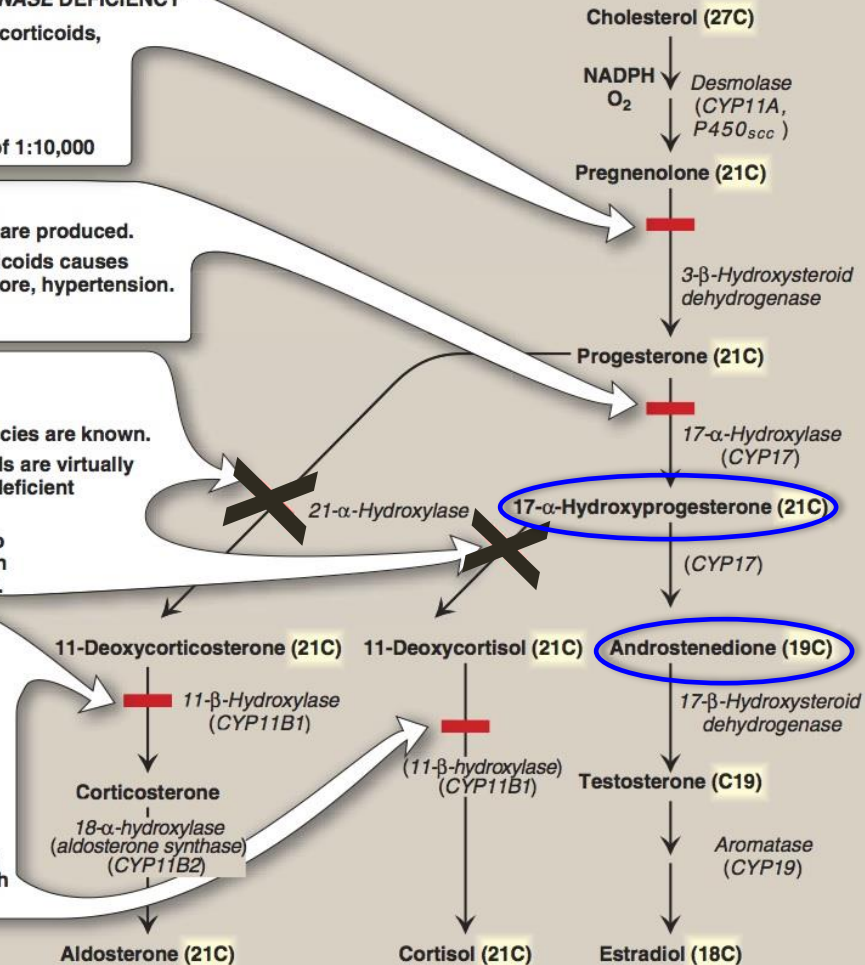
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STEROID HORMONE SYNTHESIS



In peripheral tissues

- Virilization of ♀
- Precocious sexual development in ♂

21 α -Hydroxylase Deficiency.....**CONT'D**

- Autosomal recessive condition
- Impaired synthesis of both cortisol & aldosterone
- \downarrow [cortisol] \rightarrow \uparrow ACTH secretion \rightarrow Adrenal gland hyperplasia
- Accumulated **17- α -hydroxyprogesterone** are diverted to the biosynthesis of sex hormones \rightarrow signs of androgen excess:
 - Ambiguous genitalia in newborn girls (FPH)
 - Rapid postnatal growth in both sexes
- Severe cases: mineralocorticoid deficiency \rightarrow salt & H₂O loss \rightarrow hypovolemia & shock \rightarrow neonatal adrenal crisis
- Late presentation (adult life) is possible in less severe cases

21 α -Hydroxylase Deficiency: **Genetics**

- Mutations in the CYP21 gene
 - Deletions
 - Nonsense
 - Missense
- DNA testing:
For prenatal diagnosis and confirmation of diagnosis

21 α -Hydroxylase Deficiency: **Diagnosis**

- Serum sample taken at least 2 days after birth (earlier samples may contain maternally derived 17- α -hydroxyprogesterone)
- Classic (complete) deficiency is characterized by markedly **elevated** serum levels of **17- α -hydroxyprogesterone**
- Late-onset (partial) deficiency may require corticotropin (ACTH) stimulation test:
 - Measure base-line and stimulated levels of 17- α -hydroxyprogesterone.
 - High level of 17- α -hydroxyprogesterone after stimulation is diagnostic

11 β -Hydroxylase Deficiency

leads to high concentrations of 11-deoxycortisol

Leads to high levels of 11-deoxycorticosterone with mineralocorticoid effect (salt and water retention)

Suppresses renin/angiotensin system \longrightarrow low-renin hypertension

Masculinization in females (FPH) and early virilization in males

11 β -Hydroxylase Deficiency

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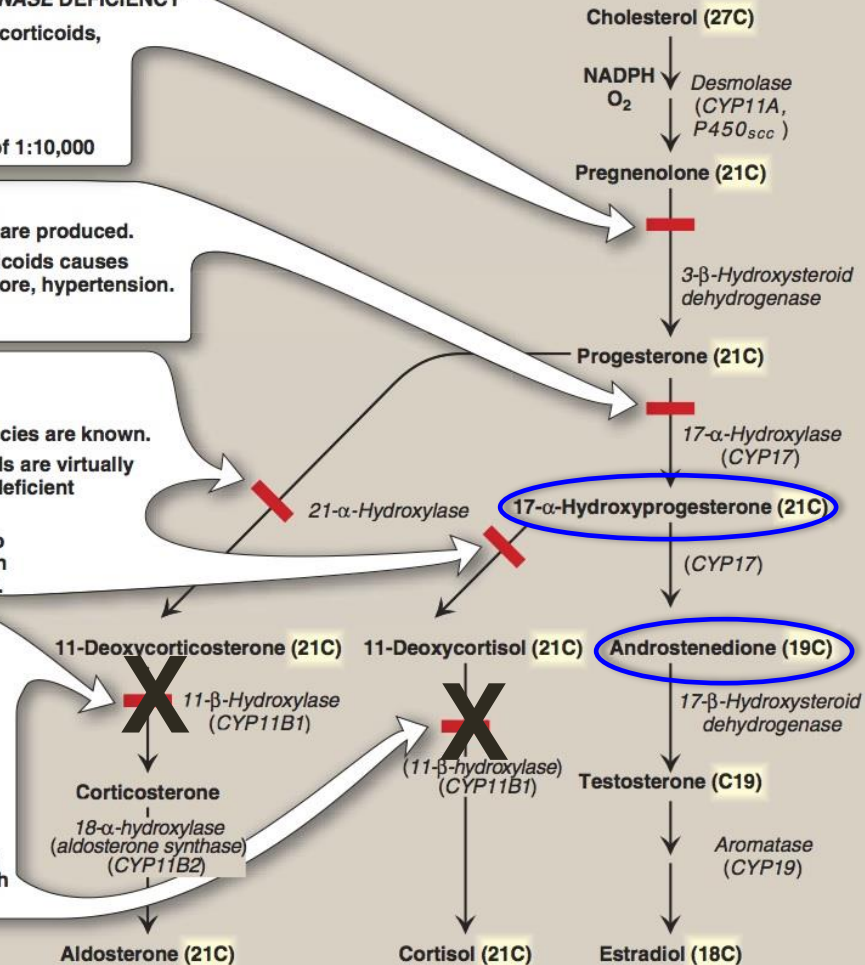
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In peripheral tissues

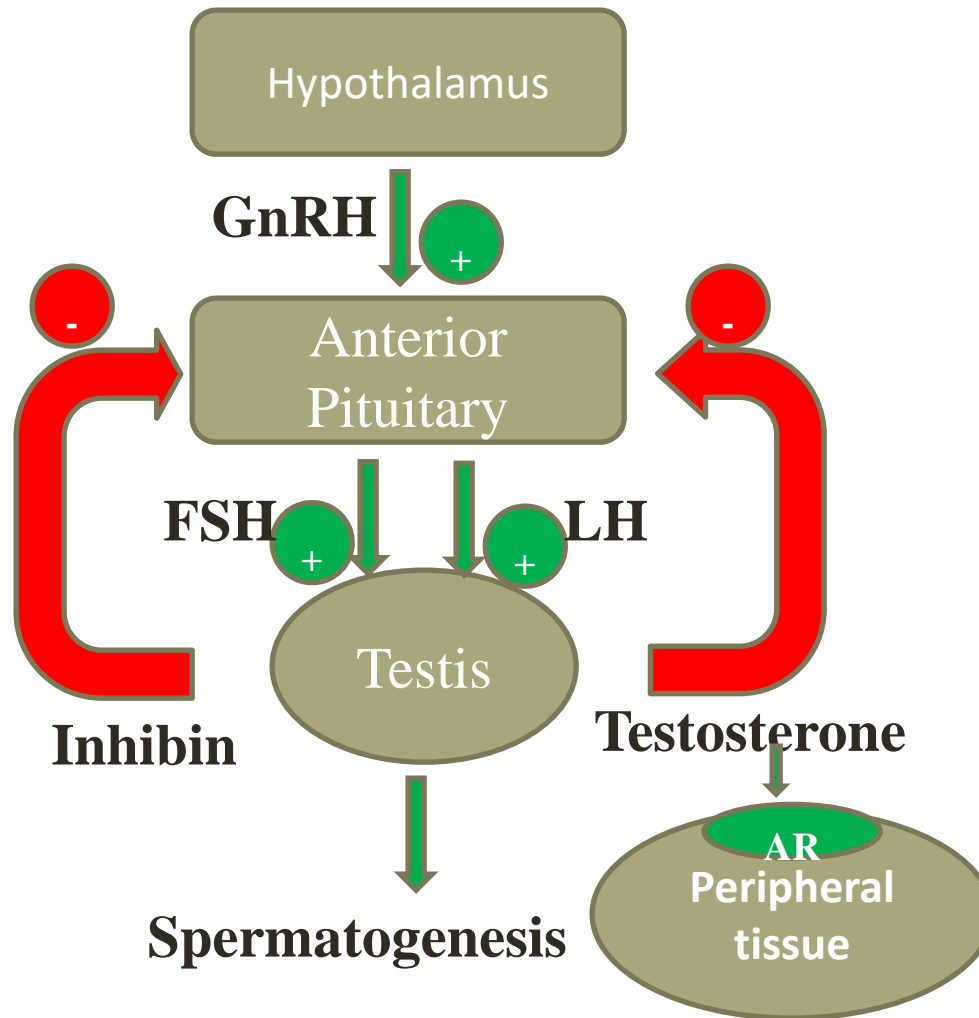
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**Testicular Feminization Syndrome
(Androgen Insensitivity
Syndrome)**

Disorders of Male Sexual Differentiation

- They are **rare** group of disorders
- The defect may be in:
 - Androgen **receptors** (inactive androgen receptors → target tissues cannot respond to stimulation by circulating testosterone; e.g., **Testicular feminization syndrome**)

Control of testicular function by the gonadotrophins



Testicular Feminization Syndrome

- 46, XY karyotype
- X-linked recessive disorder
- Androgen receptor resistance → high testosterone blood level
- In peripheral tissue, testosterone will be converted by **aromatase** into estradiol → feminization
- Patients have normal testes & produce normal amounts of müllerian-inhibiting factor (MIF), therefore, affected individuals **do not have** fallopian tubes, a uterus, or a proximal (upper) vagina.

Clinical Picture:

- **Complete androgen insensitivity syndrome (CAIS):** female external genitalia with normal labia, clitoris, and vaginal introitus (MPH)
- **Partial androgen insensitivity syndrome (PAIS):** mildly virilized female external genitalia (clitorimegaly without other external anomalies) to mildly undervirilized male external genitalia (hypospadias and/or diminished penile size)

Laboratory Diagnosis

Karyotype: differentiate an undermasculinized male from a masculinized female.

Fluorescent in situ hybridization (FISH): Presence of a Y chromosome can be confirmed by probes for the *SRY* region of the Y chromosome. These offer a much quicker turnaround time than conventional karyotypes.

Increased (or normal) testosterone and dihydrotestosterone blood levels

DNA tests and mutation analysis for androgen receptor gene:

Complete or partial gene deletions, point mutations, or small insertions/deletions

Further Investigations

Imaging Studies “Pelvic ultrasound”:

Absence of fallopian tubes and uterus

References

- Lippincott's Illustrated Reviews Biochemistry: 6th edition, Chapters 18 (Pages 219 - 244).
- Physiology of Testicular Function: shorturl.at/aMVYZ