Congenital Adrenal Hyperplasia and Testicular Feminization Syndromes

Reproductive Block

Objectives

- Adrenal steroidogenesis
- Congenital adrenal hyperplasia syndrome
    - Types
    - Biochemical characteristics
    - Clinical manifestations
- Testicular feminization syndrome

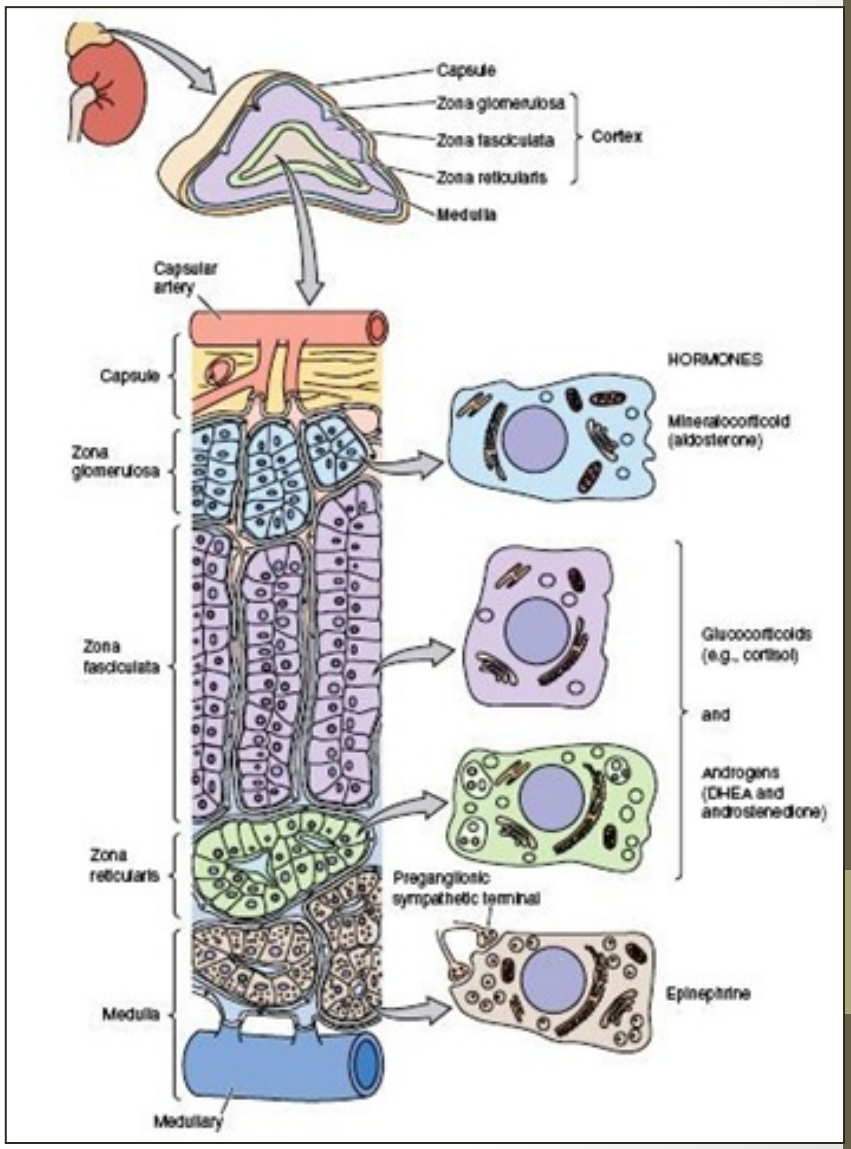
Adrenal Glands

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

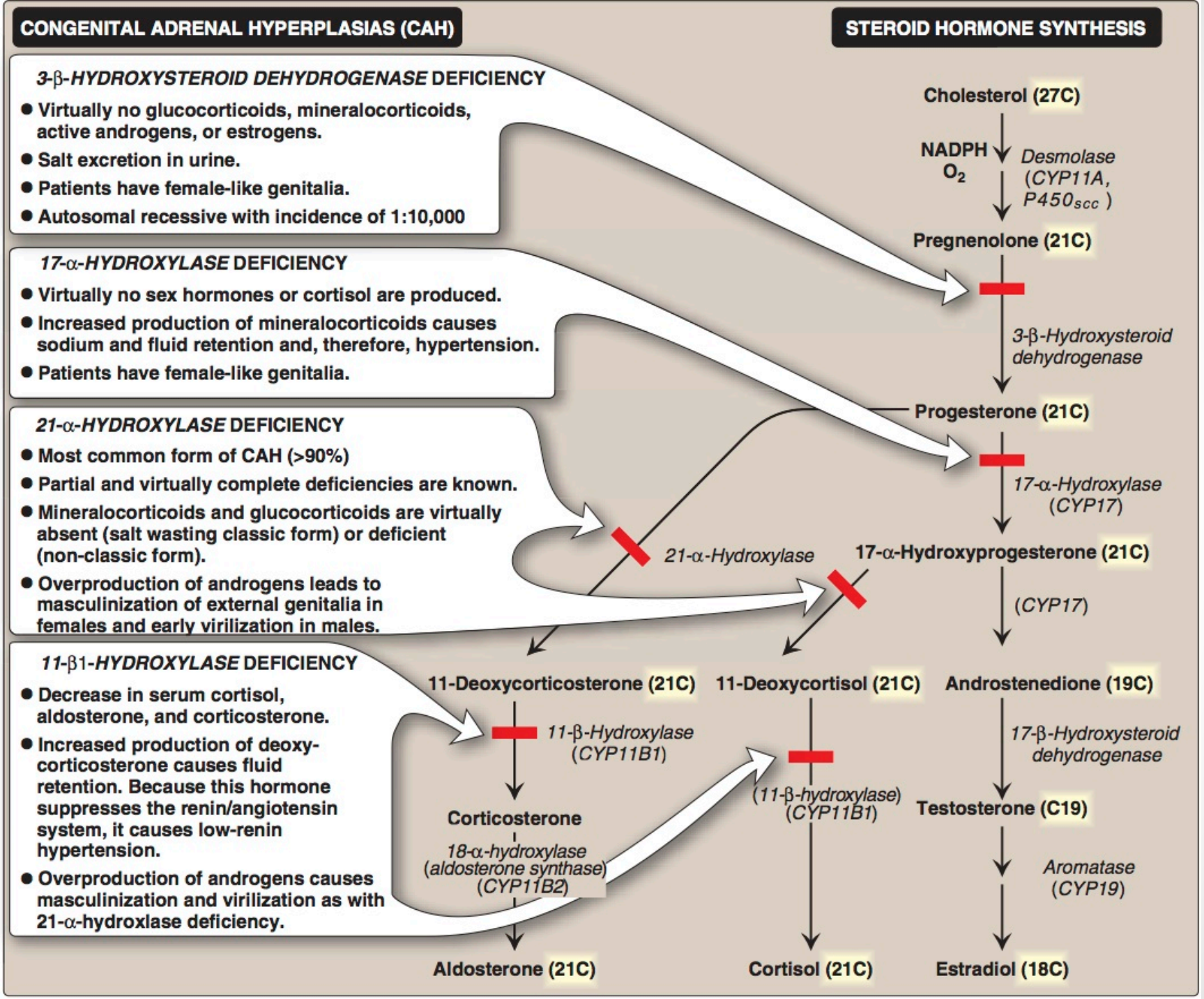
- True hermaphrodite (ovary plus testis)
- Female pseudohermaphrodite (FPH, only ovary)
- Male pseudohermaphrodite (MPH, only testis)

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)
STEROID HORMONE SYNTHESIS
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-β1-HYDROXYLASE DEFICIENCY
Decrease in serum cortisol, aldosterone, and corticosterone.
Increased production of deoxy-corticosterone 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-hydroxlase deficiency.
Cholesterol (27C)
NADPH
O2
Desmolase (CYP11A, P450scc)
Pregnenolone (21C)
3-β-Hydroxysteroid dehydrogenase
Progesterone (21C)
17-α-Hydroxylase (CYP17)
21-α-Hydroxylase
17-α-Hydroxyprogesterone (21C)
(CYP17)
11-Deoxycorticosterone (21C)
11-Deoxycortisol (21C)
Androstenedione (19C)
11-β-Hydroxylase (CYP11B1)
17-β-Hydroxysteroid dehydrogenase
(11-β-hydroxylase) (CYP11B1)
Corticosterone
Testosterone (C19)
18-α-hydroxylase (aldosterone synthase) (CYP11B2)
Aromatase (CYP19)
Aldosterone (21C)
Cortisol (21C)
Estradiol (18C)

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

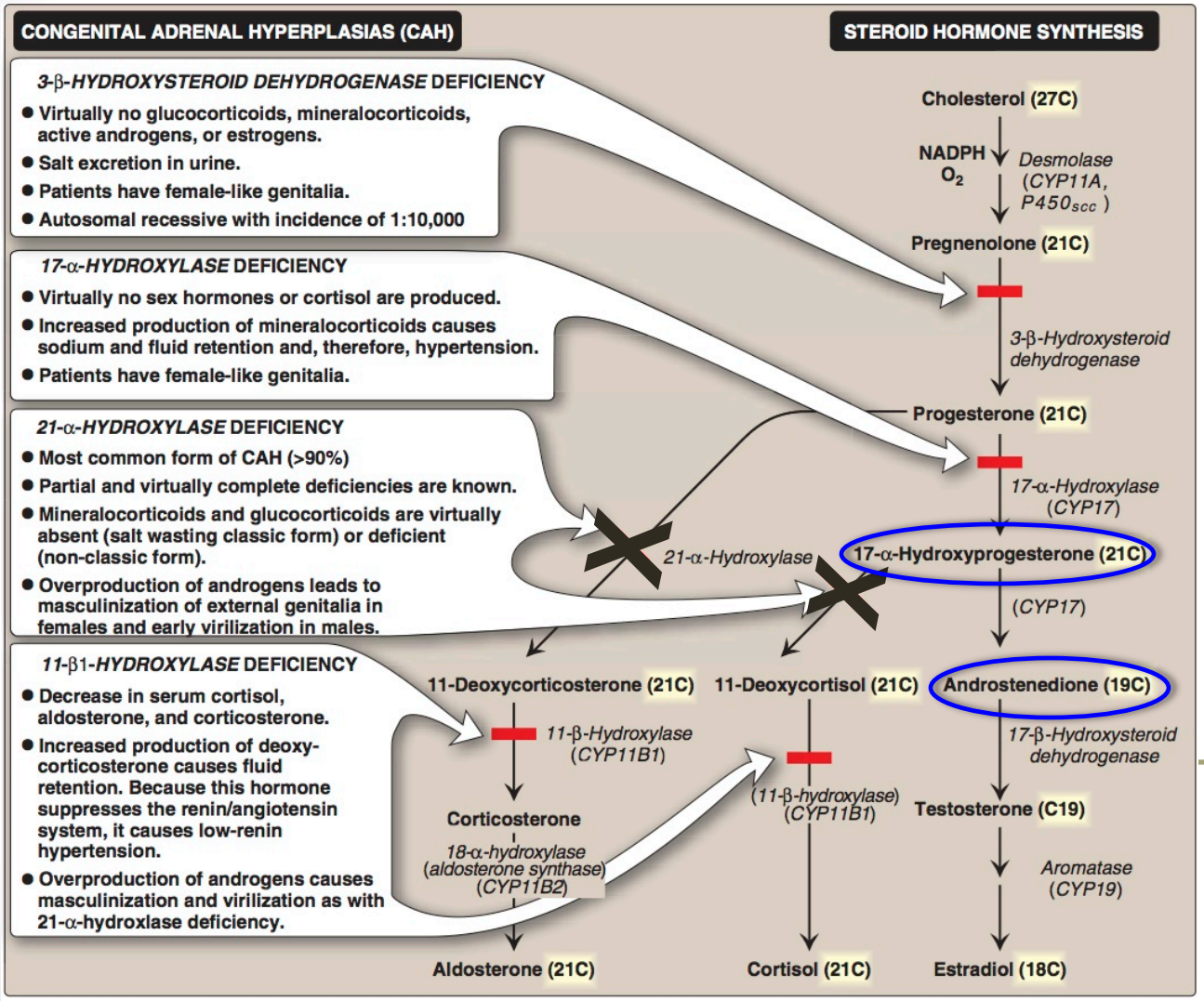
21 α-Hydroxylase Deficiency

- The most common type of CAH **(90%)**

- Clinically:
  - Complete enzyme defect: ↑ stimulation of adrenal androgen production → virilization in baby girls & precocious puberty in boys.
  - Partial enzyme defect → late onset form → menstrual irregularity & hirsutism in young females.

- Laboratory diagnosis: ↑ plasma [17-α-hydroxyprogesterone] as early as 4 days after birth

21 α-Hydroxylase Deficiency



In peripheral tissues

- Virilization of ♀
- Precocious sexual development in ♂

21 α-Hydroxylase Deficiency……CONT'D

- Autosomal recessive condition
- Impaired synthesis of both cortisol & aldosterone
- ↓ [cortisol]→↑ ACTH secretion → Adrenal gland hyperplasia
- Accumulated 17-α-hydroxyprogesterone are diverted to the biosynthesis of sex hormones →signs of androgen excess:
  - Ambiguous genitalia in newborn girls (FPH)
  - Rapid postnatal growth in both sexes
- Severe cases: mineralocorticoid deficiency → salt & H_2O loss → hypovolemia & shock → 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

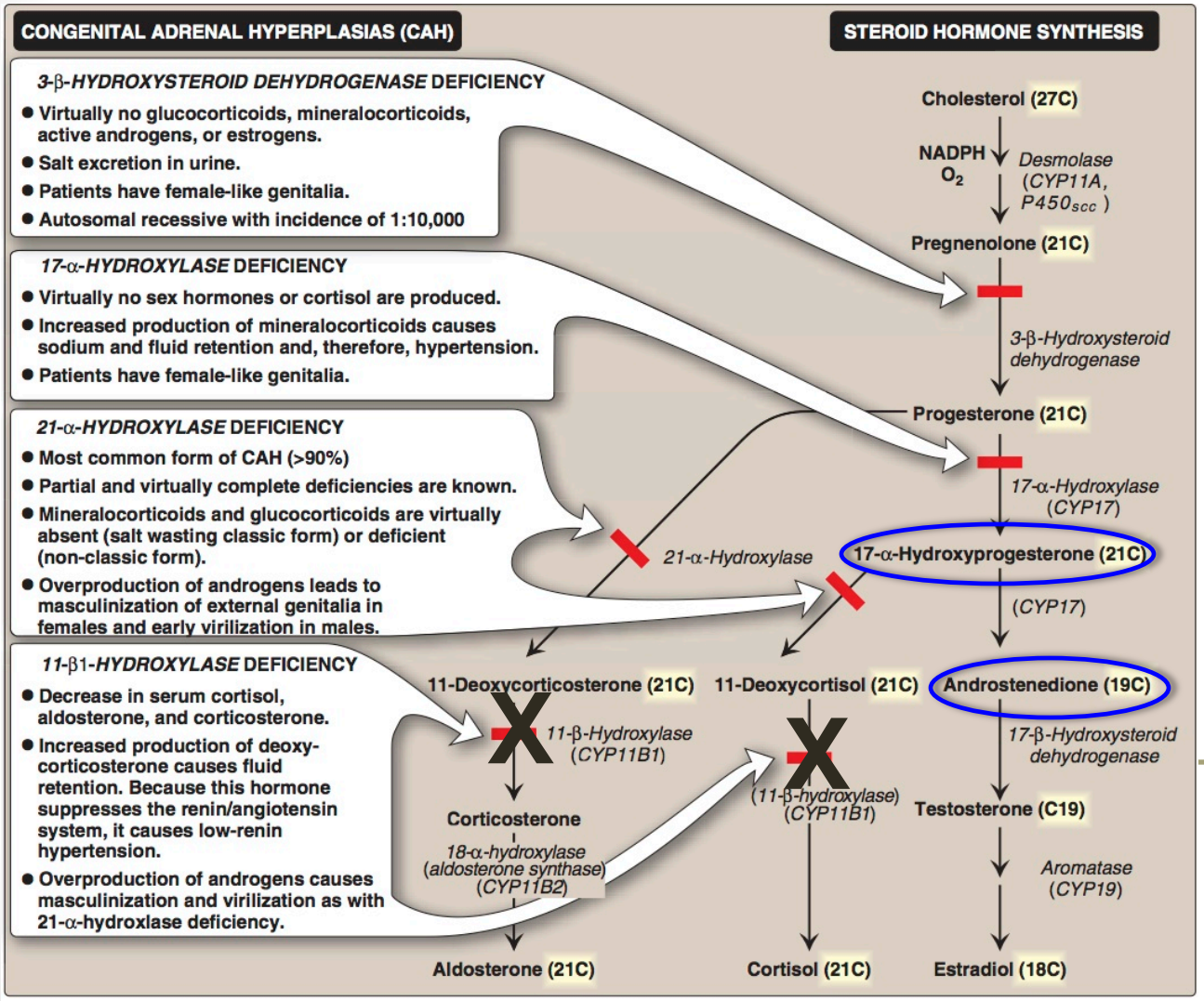
leads to high concentrations of 11-deoxycortisol

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

Suppresses renin/angiotensin system ⟶ low-renin hypertension

Masculinization in females (FPH) and early virilization in males

11 β -Hydroxylase Deficiency



In peripheral tissues

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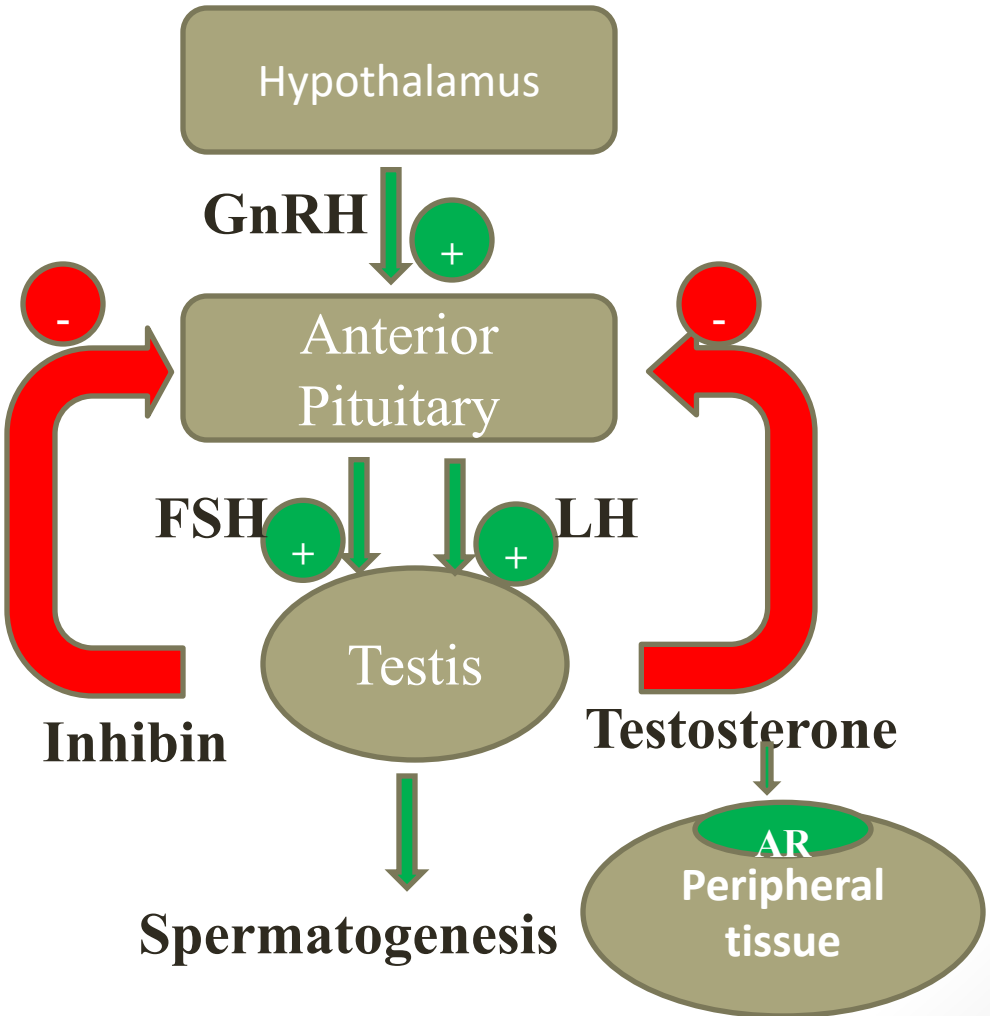
Testicular Feminization Syndrome (Androgen Insensitivity Syndrome)

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