Lecture 1:

BIOCHEMISTRY OF CONGENITAL ADRENAL HYPERPLASIA AND TESTICULAR FEMINIZATION SYNDROMES

Objectives

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

Adrenal glands

Comprise Three separate hormone systems:

1. **Zona Glomerulosa** => secretes aldosterone
2. **Zona Fasciculata & reticularis** => secrete cortisol & the adrenal androgens
3. **Adrenal Medulla** => secretes catecholamines (mainly epinephrine)

Intersex (Hermaphroditism):

- A person that has neither standard male nor standard female anatomy

(Discrepancy between type of gonads and external genitalia). 3 categories:

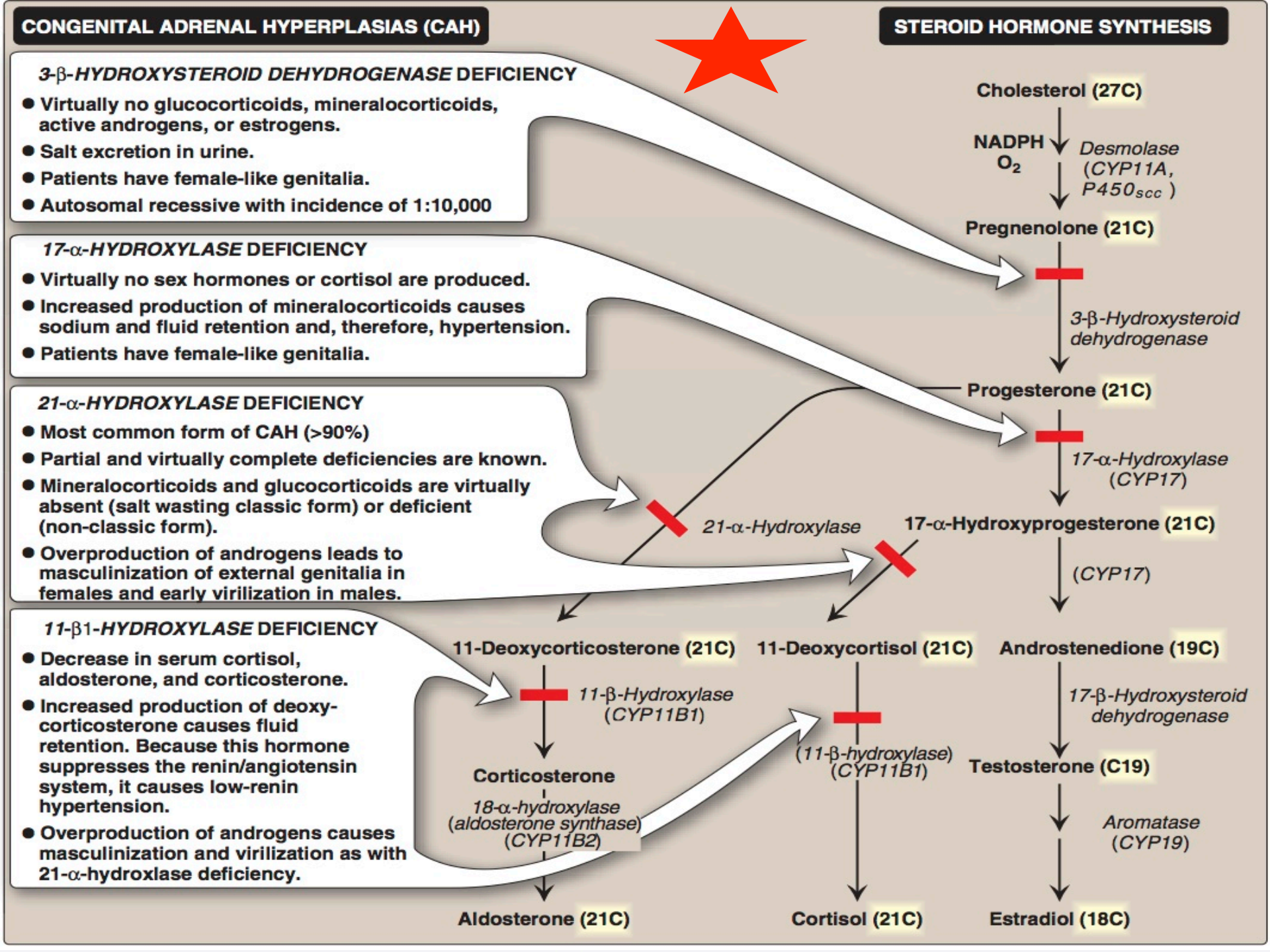
- **True hermaphrodite**: ovary plus testis
- **Female pseudohermaphrodite (FPH)**: only ovary
- **Male pseudohermaphrodite (MPH)**: only testis

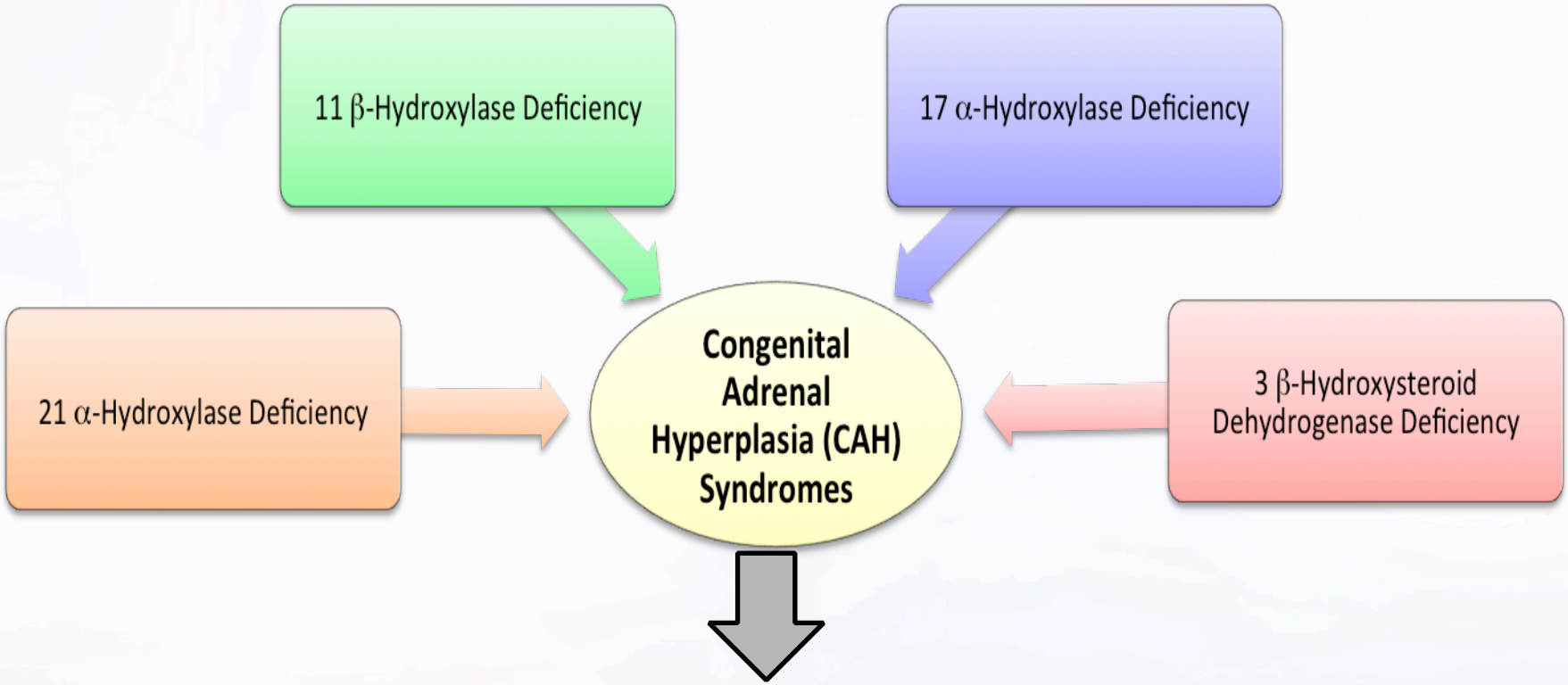
Hormones:

- ***Glucocorticoids:***

  Steroids with cortisol-like activity and are Potent metabolic regulators and immunosuppressant.
- ***Mineralocorticoids:***

  Steroids with aldosterone-like activity and Promote renal sodium reabsorption


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)



It is the result of an inherited enzyme defect in steroid biosynthesis.

1) The adrenals can not 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**)

2) The adrenals can not secrete Aldosterone => Electrolytes imbalance .

=> Hyponatremia

=> Hyperkalemia

The condition might be fatal unless diagnosed early

21 α-Hydroxylase Deficiency The most common type of CAH (90%)

- **Autosomal Recessive condition with impaired synthesis of Cortisol & Aldosterone**
- ↓ [Cortisol] => ↑ ACTH secretion

=> Adrenal gland hyperplasia

- Accumulated 17α-Hydroxyprogesterone are diverted to biosynthesis of sex hormones => Signs of excess androgen :
  1. Ambiguous genitalia in newborn girls (FPH)
  2. Rapid postnatal growth in both sexes
- In severe cases: **Mineralocorticoid deficiency**

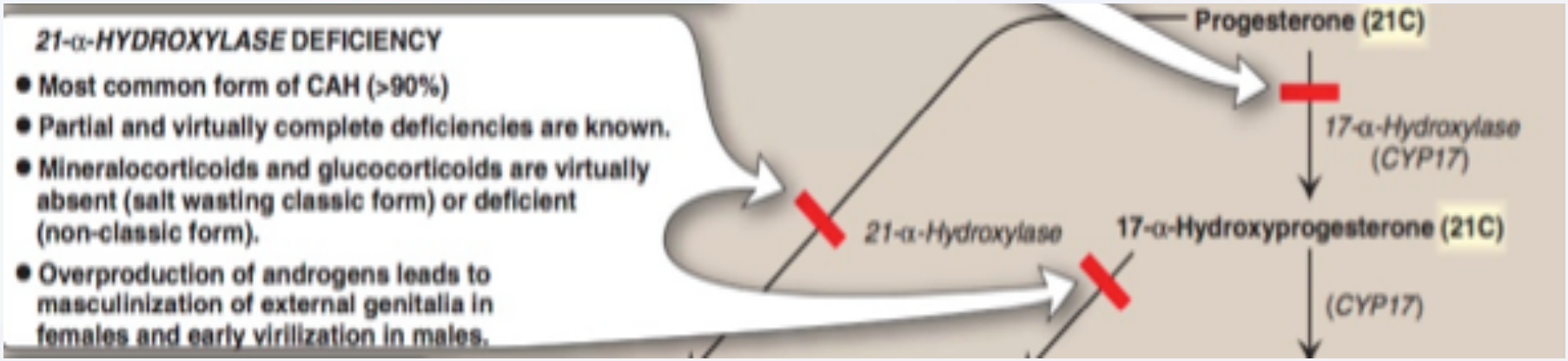
⇒ salt & H_2O loss => hypovolemia & shock

⇒ Neonatal Adrenal Crisis

- Late presentation (adult life) is possible in less severe cases

Genetics:
Mutations in the CYP21 gene
- Deletions
- Nonsense
- Missense

- **DNA testing:**
For prenatal diagnosis and confirmation of diagnosis



21 α-Hydroxylase Deficiency (CONT'D)

Clinically (2 forms)

- 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.

Diagnosis

- ↑ Plasma [17-hydroxyprogesterone] as early as 4 days after birth

N.B: Serum sample taken at least 2 days after birth (earlier samples may contain maternally derived 17-hydroxyprogesterone)

Classic (complete) deficiency

characterized by markedly **elevated serum levels of 17-Hydroxyprogesterone**

Late-onset (partial) deficiency

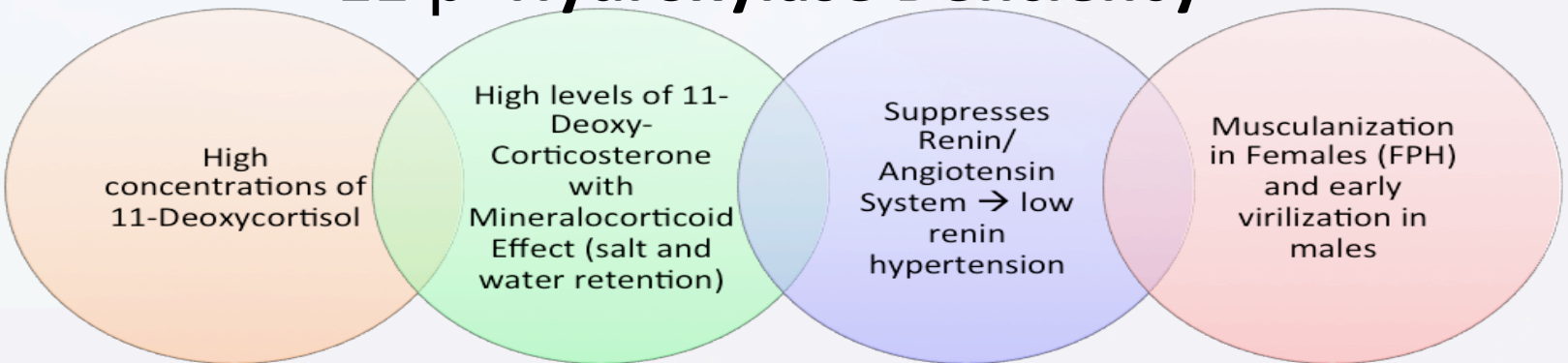
- May require Corticotropin (ACTH) stimulation test:
- PROCEDURE:

Measure base-line and stimulated levels of 17-hydroxyprogesterone.

- RESULT:

High level of 17-hydroxyprogesterone after stimulation is diagnostic

11 β -Hydroxylase Deficiency



Testicular Feminization Syndrome (Androgen Insensitivity Syndrome)

- 46, XY karyotype X-linked recessive disorder
- Androgen receptor resistance leads to high testosterone blood level.
- In peripheral tissue, testosterone will be converted by **aromatase** into estradiol leads to 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.

Disorders of Male Sexual Differentiation

- are a **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**)

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
- **Imaging Studies "Pelvic ultrasound": Absence of fallopian tubes and uterus**

Adrenogenital Syndrome

Cholesterol → Progesterone → 11-deoxy-corticosterone ("DOC") → Aldosterone

Andro-gens

Progesterone → 17-hydroxy-progesterone → 11-deoxycortisol → Cortisol

21-hydroxylase **11-β-hydroxylase**

Relative difficulty synthesizing cortisol causes more production of precursors, some of which are shunted into excess androgen production.

21-hydroxylase deficiency wastes sodium.

11-hydroxylase deficiency retains sodium since DOC is a potent mineralocorticoid.

11-DOC: 11-Deoxycorticosterone

SUMMARY

❑ **21α-Hydroxylase Deficiency (The most common type of CAH) (90%)**

- Impaired synthesis of both cortisol & aldosterone => (↑ plasma 17-hydroxyprogesterone).
- Cortisol lead to ↑ ACTH secretion lead to Adrenal gland hyperplasia
- Accumulated 17α-hydroxyprogesterone are diverted to the biosynthesis of sex hormones

❑ **11β-Hydroxylase Deficiency:**

Leads to high levels of 11-deoxy-corticosterone which has a mineralocorticoid effect (salt and water retention)

Suppresses renin/angiotensin system => low renin hypertension

Musculanization infemales (FPH) and early virilization in males (leads to high concentrations of 11-deoxycortisol).

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

- karyotype: 46,XY (X-linked recessive disorder)
- Androgen receptor resistance
- High testosterone blood level In peripheral tissue, testosterone will be converted by aromatase into estradiolà feminization.

Test yourself

1. A patient with ovary and male external genitalia has:
A. True hermaphrodite.
B. Female pseudohermaphrodite.
C. Male pseudohermaphrodite.
D. Adult type of hermaphrodite.

2. A patient with 21 a-Hydroxylase deficiency will have :
A. Hypertension.
B. Excess androgens.
C. Na retention.
D. Excess cortisol.

3. A patient with 17 a-Hydroxylase deficiency will have :
A. Less meneralcorticoids.
B. More cortisol.
C. More sex hormones .
D. Less sex hormones .

4. A patient with testicular feminization syndrome may have:
A. Low levels of cortisol.
B. High levels of testosterone.
C. increase the sensitivity of testosterone receptor .
D. Low levels of testosterone.

5. In case of Testicular Feminization Syndrome there is no fallopian tubes and no uterus because of:
A. Testosterone.
B. Dihydrotestosterone.
C. Müllerian-inhibiting factor.
D. None of the above.

6. A patient with 11- beta-Hydroxylase deficiency will have hypertension due to increase levels of :
A. Corticosterone.
B. Aldosterone.
C. Cortisol.
D. Deoxycorticosterone.

7. To diagnose Late-onset (partial) 21a-Hydroxylase deficiency we should do:
A. CRH stimulation test.
B. TSH stimulation test.
C. ACTH stimulation test.
D. GnRH stimulation test.

8. 21 a-Hydroxylase deficiency disease is :
A. Autosomal recessive.
B. X-linked recessive.
C. X-linked dominant.
D. Autosomal dominant.

9.One of the signs of androgen excess in newborns:
A. Acne.
B. Rapid postnatal growth.
C. hirsutism.
D. increase breast development.

ANSWERS: 1) B 2) B 3) D 4) B 5) C 6) D 7) C 8) A 9) B

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