STEREOLD HORMONES
BIOSYNTHESIS

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Cholesterol is the precursor of 5 classes of steroid hormones:

1. Glucocorticoids
2. Mineralocorticoids
3. Androgens
4. Estrogens
5. Progestins

Conversion of cholesterol to steroid hormones is essential for life.
The main steroid hormones include:

- **Cortisol** - a glucocorticoid
- **Aldosterone** - a mineralocorticoid
- **Estrogen** – a sex hormone
- **Testosterone** – a sex hormone
- **Progesterone** – a progestational hormone

Synthesis and secretion occurs:

- In the adrenal cortex (cortisol, aldosterone)
- Ovaries and ovarian corpus luteum (progestins, estrogens)
- Testes (testosterone)
Steroid hormones

◊ Transported by the blood from their sites of synthesis to their target cells because of their hydrophilicity

◊ Must be complexed with a plasma protein
  ▪ Plasma albumin can act as nonspecific carrier for the steroid hormones

◊ Specific plasma steroid-carrier proteins bind the steroid hormones more tightly than does albumin
  ▪ Transcortin is responsible for transporting cortisol and corticosterone
  ▪ Sex hormone-binding protein transports the sex hormones
The steroid hormones are derived from cholesterol

Progestins - regulate events during pregnancy
Glucocorticoids - promote gluconeogenesis, reduce inflammation
Mineralocorticoids - regulate ion balance via effects on kidney
Androgens - male sexual development and characteristics
Estrogens - female sexual characteristics and development

Act via nuclear receptors that control gene transcription
SYNTHESIS OF STEROID HORMONES

Conversion of cholesterol to pregnenolone

- All steroid hormones are synthesized from pregnenolone, a C\textsubscript{21} compound

- This substance results from the action of the side-chain cleavage enzyme complex (desmolase complex) on 20, 22-dihydroxycholesterol

- The process requires NADPH, oxygen, mitochondrial cytochrome P-450, adrenodoxin

Side chain requires multiple hydroxylation reactions and the reduction of molecular oxygen to water
FIGURE 12-31. Overview of steroid hormone biosynthesis. All the oxidation or hydroxylation reactions involve molecular oxygen, cytochrome P450, and NADPH.
Conversion of pregnenolone to progesterone

The conversion requires 2 activities:

◊ 3-β-ol dehydrogenase catalyses the NAD+ dependent oxidation of the alcohol to a ketone

◊ = migration

The steroid hormone pathway in the corpus lutheum of the ovary ends at progesterone
FIGURE 12–31. Overview of steroid hormone biosynthesis. All the oxidation or hydroxylation reactions involve molecular oxygen, cytochrome P450, and NADPH. The side-chain cleavage reaction leads to the formation of a five-membered ring in 20,22-dihydroxycholesterol, an intermediate in cholesterol metabolism. This reaction is catalyzed by the enzyme side-chain cleavage enzyme, which is found in the liver and intestine. The resulting five-membered ring is then oxidized to form isocaproic aldehyde, which is a precursor to pregnenolone.

Pregnenolone is a precursor to all steroid hormones and is produced by the adrenal gland, ovaries, and testes. It is converted to 17α-hydroxypregnenolone by the enzyme 17α-hydroxylase. This intermediate is then converted to 17α-hydroxyprogesterone by the enzyme 17α-hydroxylase.

17α-Hydroxyprogesterone is then converted to 17α-hydroxyprogesterone by the enzyme 17α-hydroxylase. This intermediate is then converted to progesterone by the enzyme 17α-hydroxylase.

Progesterone is then converted to dehydroepiandrosterone by the enzyme 17α-hydroxylase. This intermediate is then converted to dehydroepiandrosterone by the enzyme 17α-hydroxylase.

Dehydroepiandrosterone is then converted to androstenedione by the enzyme 17α-hydroxylase. This intermediate is then converted to androstenedione by the enzyme 17α-hydroxylase.

Androstenedione is then converted to testosterone by the enzyme 17α-hydroxylase. This intermediate is then converted to testosterone by the enzyme 17α-hydroxylase.

Testosterone is then converted to dihydrotestosterone by the enzyme 5α-reductase. This intermediate is then converted to dihydrotestosterone by the enzyme 5α-reductase.

Dihydrotestosterone is then converted to estradiol by the enzyme aromatase. This intermediate is then converted to estradiol by the enzyme aromatase.

Estradiol is then converted to estrone by the enzyme aromatase. This intermediate is then converted to estrone by the enzyme aromatase.

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The conversion of progesterone to aldosterone requires 4 reactions:

- Catalyzed by an ER 21-hydroxylase
- Mitochondrial 11-β-hydroxylase
- 18- hydroxylase
- 18-hydroxysteroid oxidase

All reactions require NADPH, O₂, cytochrome P-450
FIGURE 12-31. Overview of steroid hormone biosynthesis. All the oxidation or hydroxylation reactions involve molecular oxygen, cytochrome

The metabolism of progesterone to cortisol requires 3 reactions catalyzed by:

- ER $17\alpha$- and 21-hydroxylase
- Mitochondrial $11-\beta$-hydroxylase
FIGURE 12-31. Overview of steroid hormone biosynthesis. All the oxidation or hydroxylation reactions involve molecular oxygen. Cytochrome P450 enzymes play a key role in the hydroxylation reactions. The diagram illustrates the conversion of cholesterol to various steroid hormones, including progesterone, estrogen, and cortisol.
The metabolism of pregnenolone to testosterone require 4 ER enzymes:

- $17\alpha$ hydroxylase
- $C_{17,20}$ side chain cleavage enzyme
- $3\beta$-hydroxysteroid dehydrogenase
- $17$-hydroxysteroid dehydrogenase

The pathway ends at testosterone in the Leydig cells of the testes.
[Figure 12-31: Overview of steroid hormone biosynthesis. All the oxidation or hydroxylation reactions involve molecular oxygen, cytochrome P450, or NADPH required for the hydroxylation.](image)
The metabolism of testosterone to estradiol

- Involves the elimination of the C19 methyl group
- The conversion of ring A to an aromatic group

This process require 3 NADPH, 3 O₂, cytochrome P-450
Structure of the steroid hormones

The following describes the salient features of the various classes of steroid hormones:

- **Estradiol**: 18C and an aromatic ring
- **Testosterone**: 19C
- **Progestosterone**
- **Aldosterone** contain 21C
- **Cortisol**

Aldosterone is unique because it contains an aldehyde group on C18.
CONGENITAL ADRENAL HYPERPLASIA

Is a group of disorders arising from defects in enzymes of the adrenal cortex required for cortisol biosynthesis.

The most common enzyme defect, which accounts for 90% of the cases, is due to a deficiency of progesterone 21-hydroxylase, which is required for glucocorticoid and mineralocorticoid synthesis.

As a result:
- there is a deficiency of cortisol and aldosterone.

The plasma levels of 17-hydroxyprogesterone are greatly elevated, and there is excessive production of dehydroepiandrosterone (an androgen).
Excessive androgen production in females leads to genital ambiquity in the newborn, often requiring surgical correction.

Salt wasting and hypotension are also commonly observed.

Affected male infants have normal external genitalia and the disorder may go unrecognized in early infancy.

Androgen excess in both male and female leads to rapid growth accumulated skeletal maturation.
The incidence

of congenital adrenal hyperplasia, which is autosomal recessive disease is 1: 12,500 live birth

Affected individuals are treated with synthetic mineralocorticoids such as fludrocortisone.

These agents indirectly decrease the synthesis of pregnenolone and the formation of androgen
Steroid Synthesis

Major Pathways in Steroid Biosynthesis

- Cholesterol → 3βHSD → Pregnenolone → CYP17 → 17-hydroxy pregnenolone
- Progesterone → CYP21A2 → Deoxy-corticosterone → CYP11B1 → Corticosterone
- Aldosterone
- Cortisol
- 11-deoxycortisol → CYP11B1 → Cortisol
- 17βHSD → Estradiol
- 17βHSD → Estrone → Testosterone
- Androstenedione
- Dehydroepiandrosterone

Legend:
- Major progestagen
- Major mineralocorticoid
- Major glucocorticoid (species variation)
- Major gonadal estrogen
- Major gonadal androgen