Chapter one
Hormone Chemistry, Synthesis and Elimination

Hormones are categorized into four structural groups

- Peptides and proteins
- Steroids
- Amino acid derivatives
- Fatty acid derivatives - Eicosanoids

1.1.Peptides and Proteins

Peptide and **protein** hormones are products of **translation.** They vary considerably in size and post-translational modifications, ranging from peptides as short as three amino acids to large, multisubunit glycoproteins. Many protein hormones are synthesized as prohormones, then proteolytically clipped to generate their mature form. In other cases, the hormone is originally embedded within the sequence of a larger precursor, then released by multiple proteolytic cleavages.
Peptide hormones are synthesized in endoplasmic reticulum, transferred to the Golgi and packaged into secretory vesicles for export. They can be secreted by one of two pathways:

Regulated secretion: The cell stores hormone in secretory granules and releases them in "bursts" when stimulated. This is the most commonly used pathway and allows cells to secrete a large amount of hormone over a short period of time.

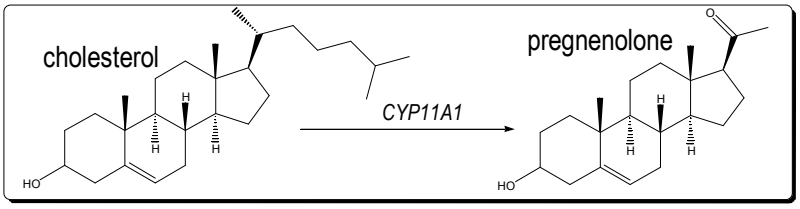
Constitutive secretion: The cell does not store hormone, but secretes it from secretory vesicles as it is synthesized.

Most peptide hormones circulate unbound to other proteins, but exceptions exist; for example, insulin-like growth factor-1 binds to one of several binding proteins. In general, the halflife of circulating peptide hormones is only a few minutes.

1.2. Steroids

Steroids are lipids and, more specifically, derivatives of **cholesterol.** Examples include the sex steroids such as testosterone and **adrenal** steroids such as cortisol. Syntheisis of steroid hormones is done by **Steroidogenesis**

Steroid hormones are derivatives of cholesterol that are synthesized by a variety of tissues, most prominently the adrenal gland and gonads. The cholesterol precursor comes from cholesterol synthesized within the cell from acetate, from cholesterol ester stores in intracellular lipid droplets or from uptake of cholesterol-containing low density lipoproteins. Lipoproteins taken up from plasma are most important when steroidogenic cells are chronically stimulated.
Biosynthesis of steroid hormones requires a battery of oxidative enzymes located in both mitochondria and endoplasmic reticulum. **The rate-limiting step in this process is the transport of free cholesterol from the cytoplasm into mitochondria.** Within mitochondria, cholesterol is converted to pregnenolone by an enzyme in the inner membrane called CYP11A1.

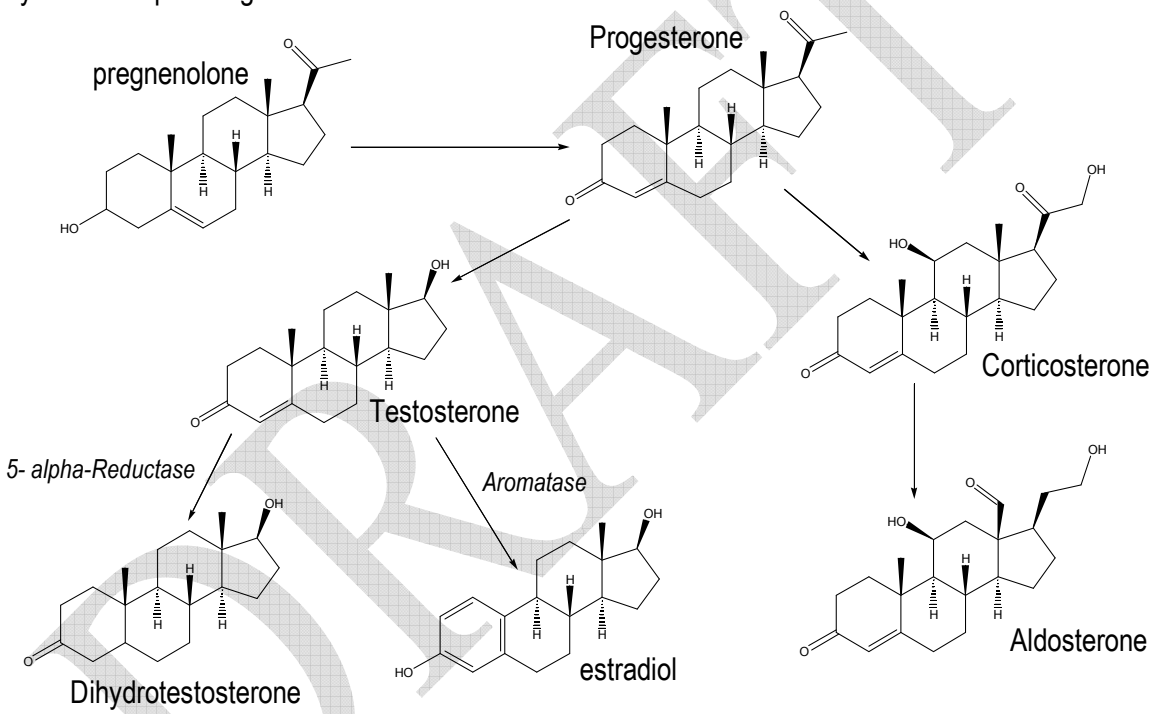


Pregnenolone itself is not a hormone, but is the immediate precursor for the synthesis of all of the steroid hormones.

Typically, endocrinologists classify steroid hormones into five groups of molecules, based primarily on the receptor to which they bind:

- **Glucocorticoids**; cortisol is the major representative in most mammals
- **Mineralocorticoids**; aldosterone being most prominent
- **Androgens** such as testosterone
- **Estrogens**, including estrodiol and estrone
- **Progestogens** (also known a progestins) such as progesterone

The biosynthetic pathways for major representatives of these classes of steroid hormones is depicted in the following diagram. Be aware that a variety of related molecules exist, some of which may have significant effects, particularly in certain pathologic conditions.

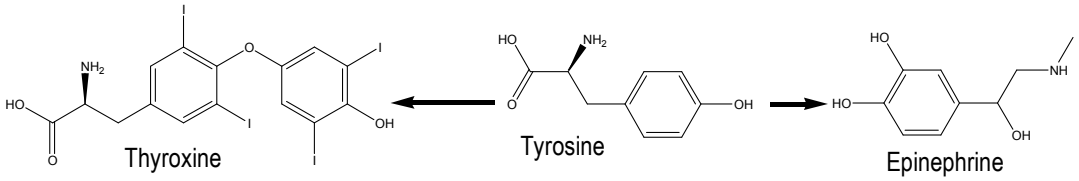


Newly synthesized steroid hormones are rapidly secreted from the cell, with little if any storage. Increases in secretion reflect accelerated rates of synthesis. Following secretion, all steroids bind to some extent to plasma proteins. This binding is often low affinity and non-specific (e.g. to albumin), but some steroids are transported by specific binding proteins, which clearly affects their halflife and rate of elimination. Steroid hormones are typically eliminated by inactivating metabolic transformations and excretion in urine or bile.

1.3. Amino Acid Derivatives

There are two groups of hormones derived from the amino acid **tyrosine:**

- **Thyroid hormones** are basically a "double" tyrosine with the critical incorporation of 3 or 4 iodine atoms.
- **Catecholamines** include **epinephrine** and **norepinephrine**, which are used as both hormones and neurotransmitters.



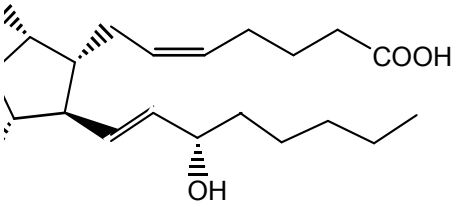
The circulating halflife of thyroid hormones is on the order of a few days. They are inactivated primarily by intracellular deiodinases. Catecholamines, on the other hand, are rapidly degraded, with circulating halflives of only a few minutes.

Two other amino acids are used for synthesis of hormones:

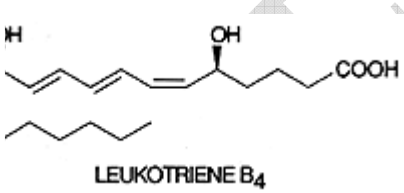
- **Tryptophan** is the precursor to **serotonin** and the pineal hormone **melatonin**
- **Glutamic acid** is converted to histamine.

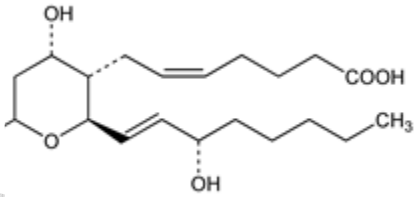
1.4. Fatty Acid Derivatives - Eicosanoids

Eicosanoids are a large group of molecules derived from polyunsaturated fatty acids. The principal groups of hormones of this class are **prostaglandins, prostacyclins, leukotrienes and thromboxanes.**



Prostaglandin F2-alpha





Arachadonic acid is the most abundant precursor for these hormones. Stores of arachadonic acid are present in membrane lipids and released through the action of various lipases. The specific eicosanoids synthesized by a cell are dictated by the battery of processing enzymes expressed in that cell. These hormones are rapidly inactivated by being metabolized, and are typically active for only a few seconds.

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