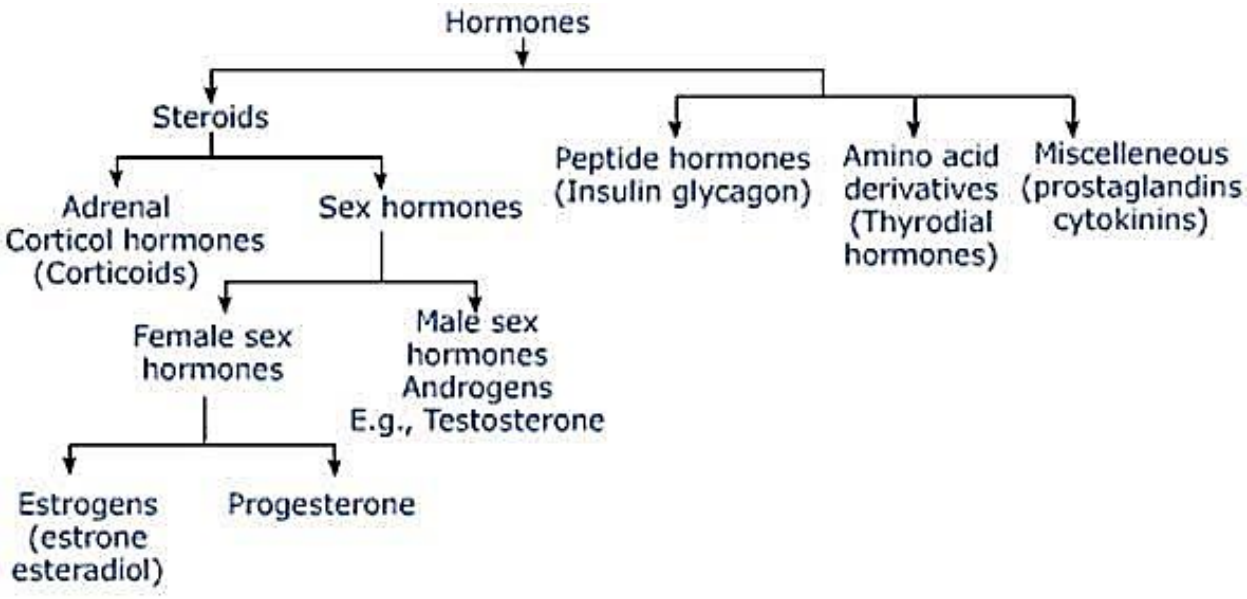
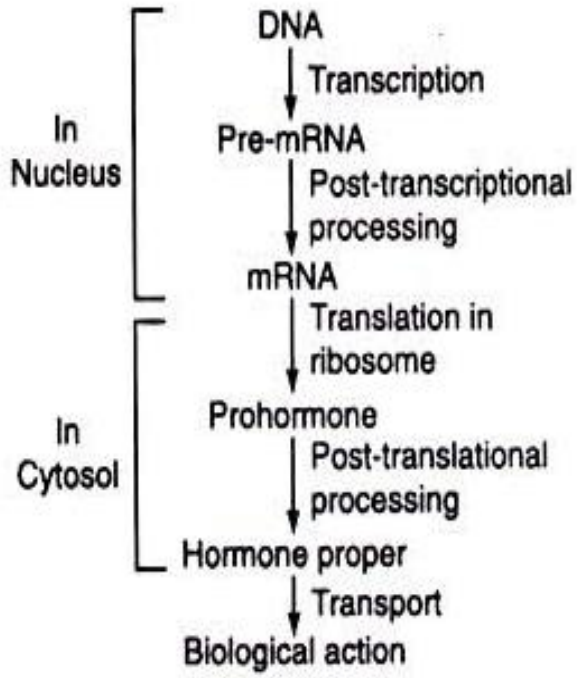
Dr. Sujan Kumar Sarkar
Lecturer
Department of Anatomy, Histology & Physiology
Sher-e-Bangla Agricultural University, Dhaka

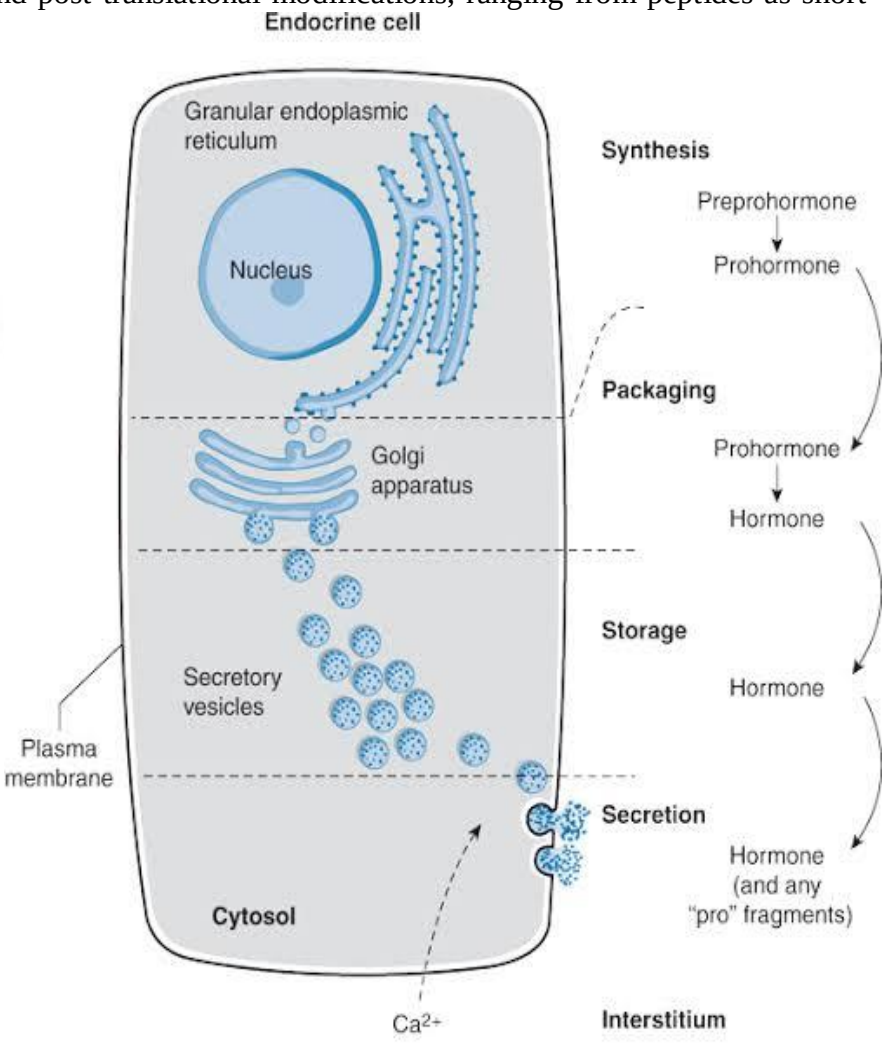
# Biosynthesis of Hormone

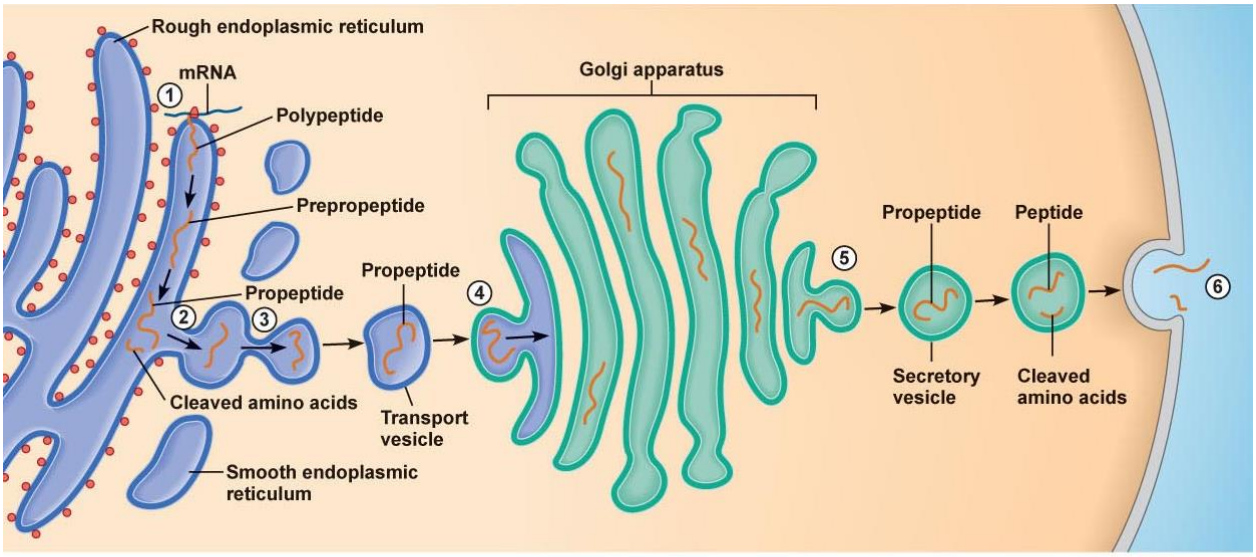



## Biosynthesis of Peptide/ Protein Hormone

- Peptides are short chains of amino acids; most hormones are peptides.
- They are secreted by the **pituitary, parathyroid, heart, stomach, liver, and kidneys**.
- They vary considerably in size and post-translational modifications, ranging from peptides as short as **three amino acids** to **large**, multi subunit glycoprotein.






- **Peptide/ Protein Hormone can be secreted by one of two pathways**
- **Types of Secretion:**
  1. **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.
  2. **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

## Biosynthesis of Steroid Hormone

- Peptide hormones are encoded by specific genes; steroid hormones are synthesized from the enzymaticaly modified cholesterol.
- Thus, there is no gene which encodes individual hormone.
- The regulation of steroidogenesis involves control of the enzymes which modify cholesterol into the steroid hormone of interest.

- Steroids **are lipids** and, more specifically, **derivatives of cholesterol**. Examples include the **sex steroids** such as testosterone and **adrenal steroids** such as cortisol.
- First step: cholesterol to pregnenolone
- **Pregnenolone** is formed on the inner membrane of **mitochondria**
- Then shuttled back and forth between **mitochondrion and the endoplasmic reticulum** for further enzymatic transformations involved in synthesis of derivative steroid hormones.

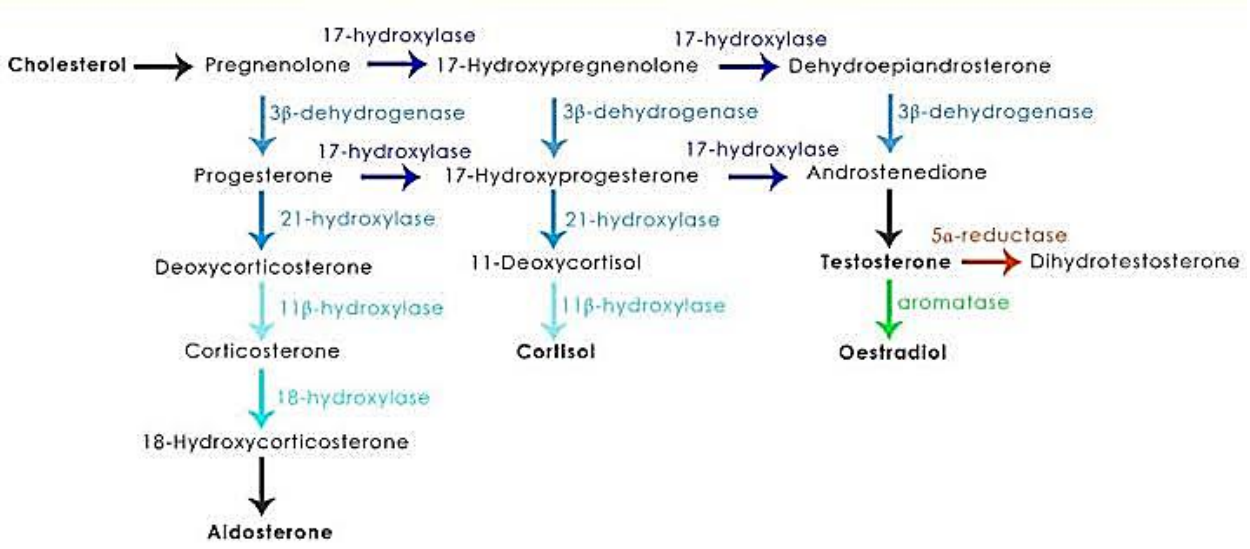
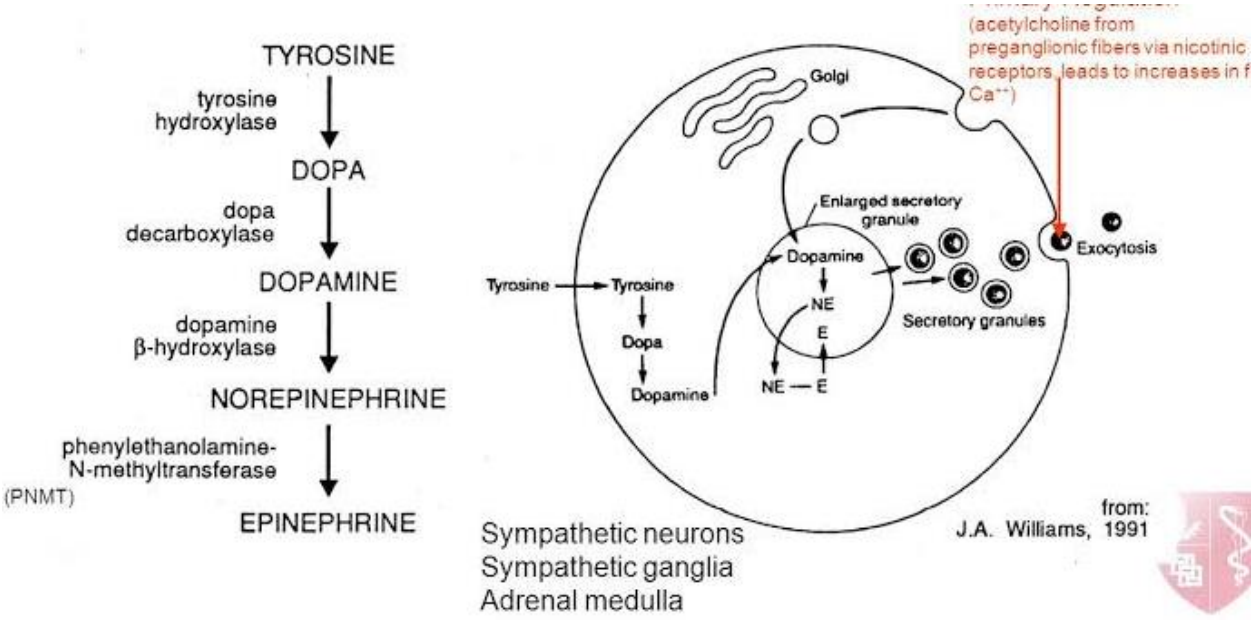



**Fig: Biosynthesis of Steroid Hormone**

# Biosynthesis of Amino Acid Derivatives

- **Amines** are derived from the amino acid tyrosine and are secreted from the **thyroid and the adrenal medulla**
- 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
- 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**



# 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.**
- **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.

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

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

**Oxytocin**

Oxytocin is a nine amino acid peptide that is synthesized in hypothalamic neurons and transported down axons of the posterior pituitary for secretion into blood. Oxytocin is also secreted within the brain and from a few other tissues, including the ovaries and testes. Oxytocin differs from antidiuretic hormone in two of the nine amino acids. Both hormones are packaged into granules and secreted along with carrier proteins called neurophysins.

**Chemistry of Thyroid Hormones**

Thyroid hormones are derivatives of the amino acid tyrosine bound covalently to iodine. The two principal thyroid hormones are:
**Thyroxine** (also known as T4 or L-3, 5, 3', 5'-tetraiodothyronine)
**Triiodothyronine** (T3 or L-3, 5, 3' -triiodothyronine)
The thyroid hormones are basically two tyrosines linked together with the critical addition of iodine at three or four positions on the aromatic rings. The number and position of the iodines is important. Several other iodinated molecules are generated that have little or no biological activity; so called "reverse T3" (3, 3', 5'-T3) is such an example.

Thyroid hormones are poorly soluble in water, and more than 99% of the T3 and T4 circulating in blood is bound to carrier proteins. The principle carrier of thyroid hormones is thyroxine-binding globulin, a glycoprotein synthesized in the liver. Two other carriers of import are transthyrein and albumin. Carrier proteins allow maintenance of a stable pool of thyroid hormones from which the active, free hormones are released for uptake by target cells.
Synthesis and Secretion of Thyroid Hormones
Thyroid hormones are synthesized by mechanisms fundamentally different from what is seen in other endocrine systems. Thyroid follicles serve as both factory and warehouse for production of thyroid hormones.

**Adrenal Steroids**
The **adrenal cortex is a factory for steroid hormones**. In total, at least two to three dozen different steroids are synthesized and secreted from this tissue, but two classes are of particular importance
Additionally, the adrenal cortex produces some sex steroids, particularly androgens, a talent of considerable importance in such diseases as congenital adrenal hyperplasia.

Like all steroids, adrenal "corticosteroids" are synthesized from cholesterol through a series of enzyme-mediated transformations. The details of these pathways are presented elsewhere, but the major branches are easy to understand.

Each of the three major pathways involves sequential processing by a group of enzymes, some of which reside in endoplasmic reticulum and others inside mitochondria. Hence, synthesis involves shuttling of the steroids between these two organelles.

Synthesis of the different steroids is not uniformly distributed through the cortex. For example, the outermost group of cells (zona glomerulosa) synthesizes aldosterone, but essentially no cortisol or androgens because those cells do not express the enzyme 17-alpha-hydroxylase which is necessary for synthesis of 17-hydroxypregnenolone and 17-hydroxyprogesterone. That enzyme is however present in cells of the inner zones of the cortex (zonae fasiculata and reticularis), which are the major sites of cortisol production.

Like all steroid hormones, cortisol and aldosterone bind to their respective receptors, and the resulting hormone-receptor complexes bind to a hormone response element to modulate transcription of responsive genes. Although the physiologic effects of these two steroid hormones are distinctly different, their receptors are quite similar and, most interestingly, they bind to the same consensus response element in DNA! How then is it possible to get hormone-specific responses? Follow the path to the next topic to find out at least part of the answer.

**Mineralocorticoids**

Removal of the adrenal glands leads to death within just a few days. Observation of such a unfortunate subject would reveal several key derangements: the concentration of potassium in extracellular fluid becomes dramatically elevated  urinary excretion of sodium is high and the concentration of sodium in extracellular fluid decreases significantly  volume of extracellular fluid and blood decrease  the heart begins to function poorly, cardiac output declines and shock ensues.

These phenomena are a direct result of loss of mineralocorticoid activity, and can largely be prevented by replacement of salts and mineralocorticoids. Clearly mineralocorticoids are acutely critical for maintenance of life.

**Biosynthesis of Insulin**

Insulin is synthesized in significant quantities only in beta cells in the pancreas. The insulin mRNA is translated as a single chain precursor called preproinsulin, and removal of its signal peptide during insertion into the endoplasmic reticulum generates proinsulin.

Pro-insulin consists of three domains: an amino-terminal B chain, a carboxy-terminal A chain and a connecting peptide in the middle known as the C peptide. Within the endoplasmic reticulum, proinsulin is exposed to several specific endopeptidases which excise the C peptide, thereby generating the mature form of insulin. Insulin and free C peptide are packaged in the Golgi into secretory granules which accumulate in the cytoplasm.

When the beta cell is appropriately stimulated, insulin is secreted from the cell by exocytosis and diffuses into islet capillary blood. C peptide is also secreted into blood, but has no known biological activity.