Ministry of Public Health of Ukraine
Zaporizhzhia State Medical University
Biological Chemistry Department

Biochemistry of Hormones

(Module 2, IV Semester)

Textbook
for independent work at home and in class
for students of international faculty

Speciality: 7.120 10001 «General Medicine»

Zaporizhzhia, 2015

Textbook was confirmed on the Central Methodological Commission of ZSMU as manual for «Biological chemistry» discipline for students of second year education of international faculty speciality: 7.120 10001 «General Medicine»

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Biochemistry of hormones : Textbook for independent work at home and in class for students of medical faculty Speciality: 7.120 10001 «General Medicine» / ed. : K. V. Aleksandrova, S. V. Levich, D. G. Ivanchenko. – Zaporizhzhia : ZSMU 2015. - 77 p.

Textbook was made in accordance with the program of biological chemistry for training of students of higher educational institutions of III-IV levels of accreditation for specialty 7.12010001 «General Medicine».

This textbook is recommended to use for students of international department (the second year of study) for independent work at home and in class.

CONTENT

ABSTRACT

Hormones - biologically active substances, which released into the blood by the endocrine glands and humoral way (through blood, lymph, saliva, cerebrospinal fluid). They regulate metabolism and physiological processes. Hormones, as universal regulators of the body functioning, play an important role in the maintenance of homeostasis. They influence on all essential life processes, such as: growth, metabolism, development, immune defense, reproduction, behavior and adaptation to the conditions of existence.

The hormonal effects on metabolic processes of target cells are realized through interaction with specific receptors. Depending on the localization of these receptors different mechanisms of action of hormones are presented.

This textbook contains all necessary information about structure, classification, mechanisms of action and biological effects of all main hormones in human organism and can be used for preparation for practical lessons of biological chemistry for student of medical .

CLASSIFICATION OF HORMONES

The term hormone (*hormao*[G] = to excite) was first used by William M. Bayliss and his brother-in-law Ernest H. Starling, both of London University College, in 1904, who showed that a chemical substance (*secretin*) from the intestine could stimulate the action of a pancreatic secretion. These substances were then called as 'chemical messengers'. Went and Thimann (1937) defined a hormone as *"a substance which, produced in any one part of an organism, is transferred to another part and there influences a specific physiological process."*

The tissues or organs where they are produced are called as **effectors** and those where they exert their influence as **targets.**

Based on their site on action, the hormones are of two types : local and general. The *local hormones,* obviously, have specific local effects, whence their nomenclature. These may be exemplified by acetylcholine, secretin, cholecystokinin etc. The *general hormones*, on the other hand, are secreted by specific endocrine glands and are transported in the blood to cause physiologic actions at points remote from their place of origin. A few of the general hormones affect almost all cells of the body, *e.g*., growth hormones (GH) and thyroid hormones ; whereas other general hormones, however, affect specific tissues far more than other tissues, *e.g*., adrenocorticotropin (a hormone secreted from adenohyprophysis and stimulating the adrenal cortex) and ovarian hormones (affecting the uterine endometrium).

The hormones conduct a wide variety of functions ranging from growth, vegetative and sexual development, cellular oxidation to thermal production and the metabolism of carbohydrates, proteins and fats. The various functions performed by hormones may, in general, be discussed under following heads:

1. Regulatory or homeostatic function. The hormones have regulatory effects on the composition of the body fluids, the rate of gaseous exchange and the activity of the vascular system and the central nervous system (CNS). There always exists a high degree of precision and constancy in the composition of the body fluids in a normal individual for the conduction of various activities.

2. Permissive function. Not only does each endocrine gland affect a number of processes, but these glands also affect the functioning of one another. Thus certain hormones require the presence (or 'permission') of another hormone for the expression of their activity. This helps in maintaining a perfect hormonal balance. Derangements of this balance, either clinical or experimental, lead to a variety of metabolic aberrations.

3. Integrative function. The integrative function of the hormones is reflected in the fact that they support the role of nervous system. However, the integrative properties of the endocrine system are slow and steady whereas those of the nervous system are rapid. This close tie between the two systems has led to the emergence of a new discipline of science called *neuroendocrinology.*

4. Morphogenetic function. The hormones govern the ontogenetic development of an individual from the embryonic to the adult state.

Chemically, a hormone may be any kind of organic molecule. Most known hormones are either **steroids** or **peptides** with usually high molecular weights. A third group of hormones, which is less common, consists of **amino acid derivatives** (or phenolic derivatives) with relatively low molecular weights. Thus, three categories of hormones may be recognized: steroids, peptides and amino acid derivatives (figure 1).

Vertebrate Hormones

STEROID HORMONES	PEPTIDE HORMONES	AMINO ACID HORMONES
C_{18} STEROIDS		
1. Ovarian Hormones	**1. Hormones of the Pancreas**	**1. Thyroidal Hormones**
β-estradiol	Insulin	Triiodothyronine, T_3
Estriol	Glucagon	Tetraiodothyronine T_4
Estrone		
C_{19} STEROIDS		
2. Testicular Hormones	**2. Hormones of the Hypophysis**	**2. Adrenal Medullary**
From testes	*Pars distalis*	*Hormones*
Testosterone	Thyrotropin, TSH	Adrenalin
Androsterone	Corticotropin, ACTH	Noradrenalin
Dehydroepiandrosterone	Gonadotropins, GTH	
	FSH	
From adrenal gland	LH	
Androst-4-ene-3,17,dione	LTH	
Androst-4-ene-3,11,17-trione	Somatotropin, SH	
C_{21} STEROIDS	*Pars intermedia*	
3. Adrenal Cortical Hormones	Intermedins, MSH	
Mineralocorticoids	α-MSH	
Aldosterone	β-MSH	
Deoxycorticosterone		
Glucocorticoids	*Pars nervosa*	
Cortisone	Ocytocin or pitocin	
Cortisol	Vasopressin or pitressin	
Corticosterone		
	3. Hormone of the Parathyroid	
	Parathormone, PTH	
4. Corpus Luteal Hormone	**4. Hormones of the Gastrointestinal Tract**	
Progesterone	Gastrin	
	Secretin	
	Cholecystokinin	
	Pancreozymin	
	Enterogastrone	
	Enterokrinin	
	Hepatocrinin	
	Duicrinin	
	Villikinin	
	Parotin	
	5. Hormone of the Corpus Luteum	
	Relaxin	

Figure 1. Classification of hormones by chemical nature

MECHANISMS OF HORMONE ACTION

The function of different hormones is to *control* the activity of levels of target tissues. To achieve this, the hormones may alter either the permeability of the cells or they may activate some other specific cellular mechanism. Although the exact site of action of any hormone is not established, five *general sites* have been proposed.

A. Hormonal Action at Cyclic Nucleotides Level. Many hormones exert their effect on cells by first causing the formation of a substance, cyclic 3′, 5′-adenosine monophosphate (figure 2) in the cell.

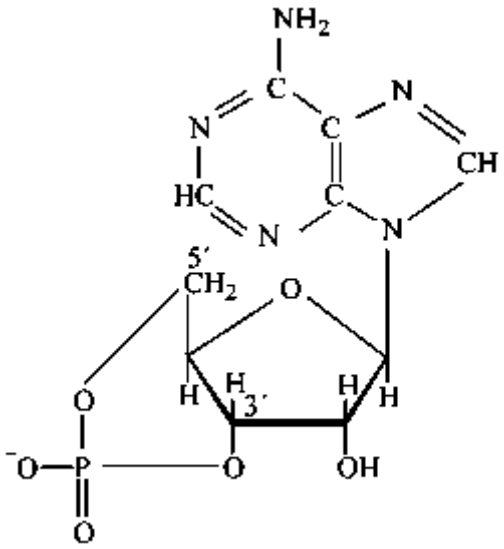


Figure 2. Cyclic 3′, 5′-adenosine monophosphate, cAMP

Once formed, the cyclic AMP causes the hormonal effects inside the cell. Thus, *cyclic AMP acts as an intracellular hormonal mediator*. It is also frequently referred to as the *second messenger* for hormone mediation; the *first messenger* being the original hormone itself.

The effects of cyclic AMP on the action of a hormone was first described by Earl W. Sutherland and T.W. Rall in 1960. They found that the effect of epinephrine on hepatic glycogenolysis (breakdown of glycogen) is a result of the

conversion of inactive phosphorylase b into an active form by cyclic AMP. Epinephrine was found to activate the enzyme, adenyl cyclase which, in turn, converts ATP to cAMP. Besides epinephrine, other hormones like glucagon, parathormone, ACTH, TSH, ICSH, LH, α-MSH and vasopressin are now known to have a stimulatory effect on cAMP levels. Several hormones, on the contrary, decrease cAMP levels and thus produce an opposite effect. These include insulin, melatonin and the prostaglandins. From the many names of hormones given above, it appears that hormone action not mediated by cAMP may be an exception rather than the rule.

Figure 3 depicts, in a schematic way, the effect of cAMP on hormone action. The cell contains receptor for hormones in the plasma membrane. The stimulating hormone acts at the plasma membrance of the target cell and combines with a specific receptor for that particular type of hormone. The specificity of the receptor determines which hormone will affect the target cell. The combination of the hormone with its receptor leads to the activation of the enzyme, adenyl cyclase, which is also bound to the plasma membrane. The portion of the adenyl cyclase that is exposed to the cytoplasm causes immediate conversion of cytoplasmic ATP into cAMP. The reaction representing cAMP synthesis may, thus, be written as:

$$\text{ATP} \rightarrow \text{cAMP} + \text{PP}_\text{i} + \text{H}^+$$

The reaction is slightly endergonic and has a $\Delta G^{\circ\prime}$ value of about 1.6 kcal/mol.

The cAMP then acts inside the cell to initiate a number of cellular functions before it itself is destroyed. The various functions initiated include:

(*a*) activating the enzymes

(*b*) altering the cell permeability

(*c*) synthesizing the intracellular proteins

(*d*) contracting or relaxing the muscles

(*e*) releasing other hormones (*third messengers*).

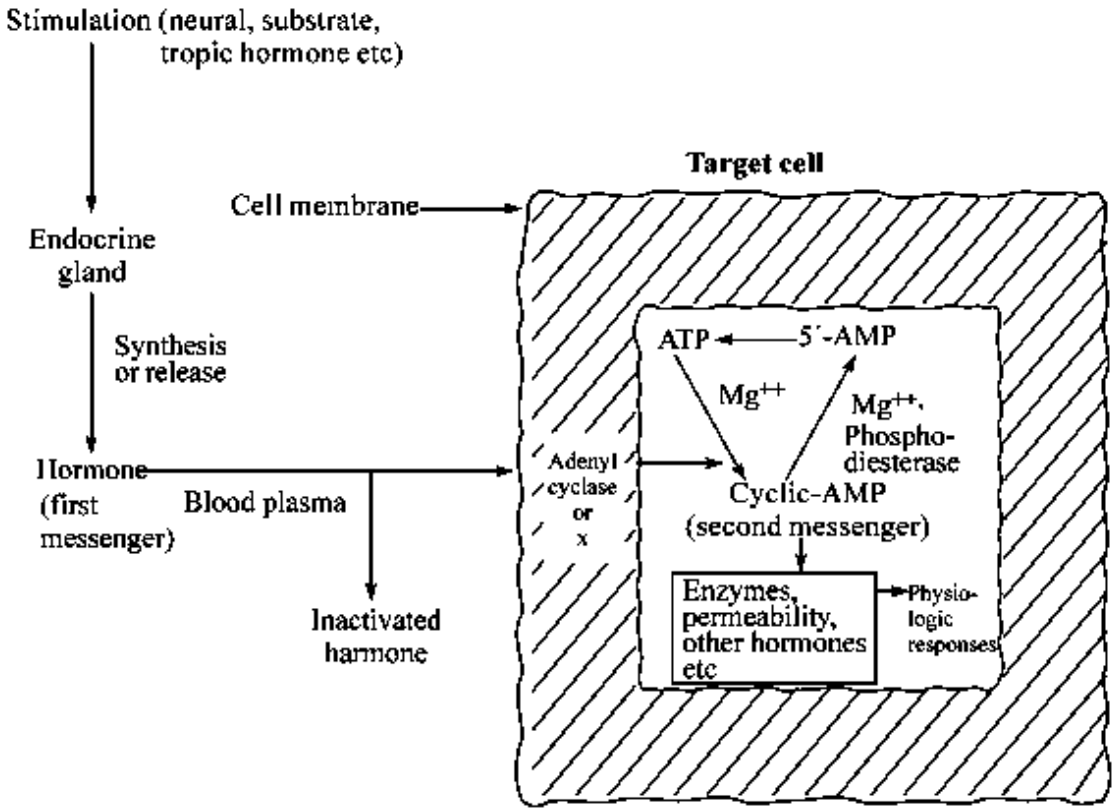


Figure 3. Role of cAMP

It should, however, be emphasized that *what cAMP does in a particular effector cell is determined by the cell itself, rather than by cAMP.*

Cyclic AMP is, however, destroyed (or inactivated) by a specific enzyme called *phosphodiesterase*, which hydrolyzes it to AMP. Like adenyl cyclase, the phosphodiesterase is present in practically all tissues.

$$\text{Cyclic AMP} + H_2O \xrightarrow{Mg^{2+}} \text{AMP} + H^+$$

This reaction is highly exergonic, having a $\Delta G^{\circ\prime}$ value of about –12 kcal/mol.

Cyclic AMP is a very stable compound unless hydrolyzed by a specific phosphodiesterase. An important feature of the second messenger model is that *the hormone need not enter the cell and its impact is made at the cell membrane*. The biological effects of the hormone are mediated inside the cell by cAMP rather than by the hormone itself. *cAMP and the Protein Kinases* — Cyclic AMP elicits many of its effects by activating protein kinases. Protein kinases are ubiquitous in nature

and are activated by cAMP at extremely low concentrations of 10–8 M. These kinases molecule the activities of different proteins in different cells by phosphorylating them. The enzyme *protein kinase* (figure 4) consists of two subunits: a catalytic subunit and a regulatory subunit which can bind cAMP. In the absence of cAMAP, the catalytic and regulatory subunits form a complex that is enzymatically inactive.

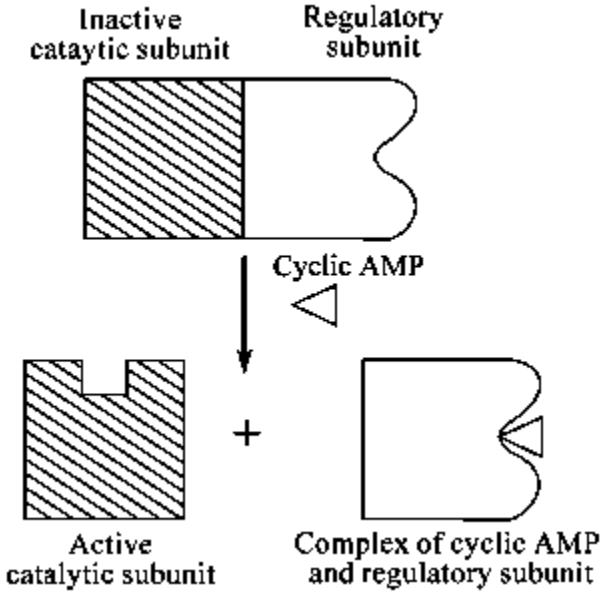


Figure 4. Influence of cAMP on Protein kinase

In the presence of cAMP, however, the complex disintegrates, freeing the catalytic subunit which now becomes catalytically active. The regulatory subunit binds cAMP to form a complex. Thus, the binding of cAMP to the regulatory subunit relieves its inhibition of the catalytic subunit. The cAMP acts as an allosteric effector.

Other Intracellular Hormonal Mediators — It has been postulated that, besides cAMP, other types of intracellular hormonal mediators also exist.

1. One almost-certain mediator is **cyclic guanosine monophosphate** (= cyclic GMP). Cyclic GMP is a nucleoside similar to cAMP and is found in most tissues. It can probably catalyze some intracellular functions in a manner similar to that of cAMP.

2. Another type of intracellular hormonal mediator is a group of compounds referred to as **prostaglandins**. These substances frequently cause intracellular inhibition, in contrast to the activation usually caused by cAMP.

B. Induction of Enzyme Synthesis at the Nuclear Level. A second major mechanism by which the hormones, *esp*., the steroidal and thyroidal ones, act is to cause synthesis of proteins in the target cell. These proteins are presumably the enzymes which, in turn, activate other functions of the cells. The mechanism behind the **steroidal hormones** is depicted in figure 5.

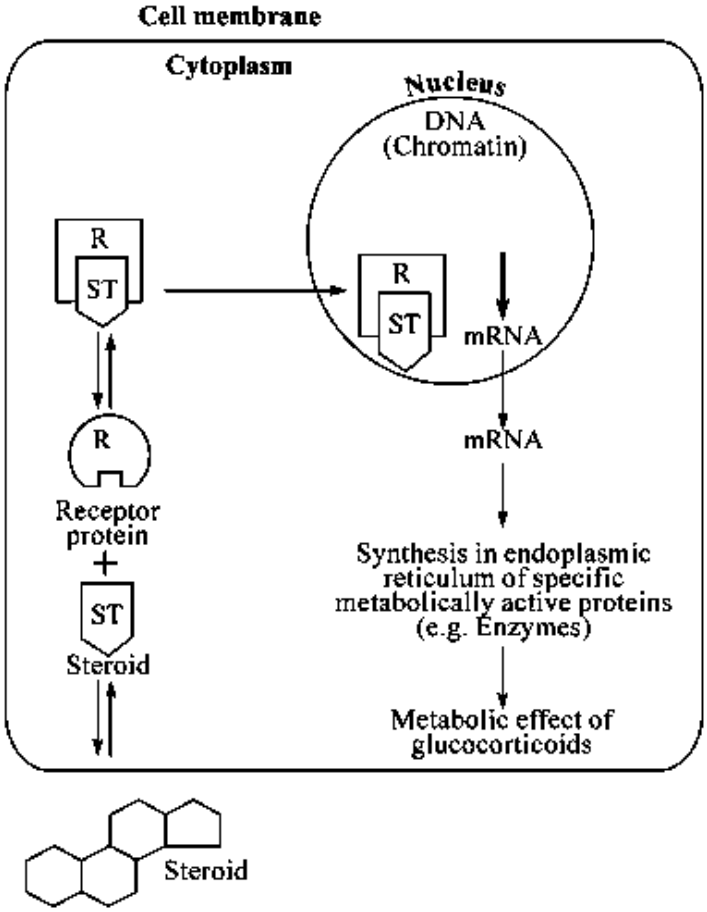


Figure 5. Mechanism of action of steroidal hormones

The sequence of events is as follows :

1. The steroidal hormone enters the cytoplasm of the target cell where it binds with a specific, high- affinity receptor protein.

2. The receptor protein- hormone complex, so formed, then diffuses into (or is transported into) the nucleus, where it reacts with the nuclear chromatin.

3. Somewhere along this route, the receptor protein is structurally altered to form a smaller protein with low molecular weight. Or else the steroid hormone is transferred to a second smaller protein.

4. The combination of the small protein and hormone is now the active factor that stimulates the specific genes to form messenger RNA (mRNA) in the nucleus.

5. The mRNA diffuses into the cytoplasm where it accelerates the translation process at the ribosomes to synthesize new proteins. It is, however, noteworthy that a direct chemical reaction of the hormone with DNA or RNA polynucleotide is not likely. Instead, the hormone must first combine with a specific receptor protein and it is this combination that acts on DNA chromatin. It is possible that the chromatin proteins may influence hormonal activity by modifying the ability of the receptor complex to bind with DNA.

To cite an example, the aldosterone, one of the mineralocorticoids secreted by adrenal cortex, enters the cytoplasm of the renal tubular cells. These tubular cells contain its specific receptor protein and hence above sequence of events follows. After about 45 minutes, the proteins begin to appear in the renal tubular cells that promote sodium reabsorption from the tubules and potassium secretion into the tubules. This characteristic delay, of about 45 minutes, in the final action of this steroid hormone is in marked contrast to the almost instantaneous action of some of the peptide hormones.

The **thyroidal hormones** act similarly to enhance RNA and enzyme synthesis but may do so by directly binding with the specific receptor proteins present in the nuclear chromatin. The receptors present in the cytoplasm are less effective in this regard.

C. Stimulation of Enzyme Synthesis at Ribosomal Level. In the case of some hormones, the activity is at the level of translation of information carried by the mRNA on the ribosomes to the production of enzyme protein. For example, the

ribosomes taken from animals, which have been given growth hormone, have a capacity for protein synthesis in the presence of normal mRNA.

D. Direct Activation at the Enzyme Level. It has been experimentally observed that treatment of the intact animal (or of isolated tissue) with some hormones results in a change in enzyme behavior which is not related to *de novo* synthesis. The cell membrane is usually required for such activity. Henceforth, it is possible that activation of a membrane receptor might be an initial step in hormone action.

E. Hormone Action at the Membrane Level. Many hormones appear to transport a variety of substances, including carbohydrates, amino acids and nucleotides, across cell membranes. These hormones, in fact, bind to cell membranes and cause rapid metabolic changes in the tissues.

Catecholamines (epinephrine and norepinephrine) and many protein hormones stimulate different membrane enzyme systems by direct binding to specific receptors on cell membrane rather than in the cytoplasm.

A schematic representation of the two principal mechanisms of action involving water soluble hormones and steroid hormones is presented in figure 6.

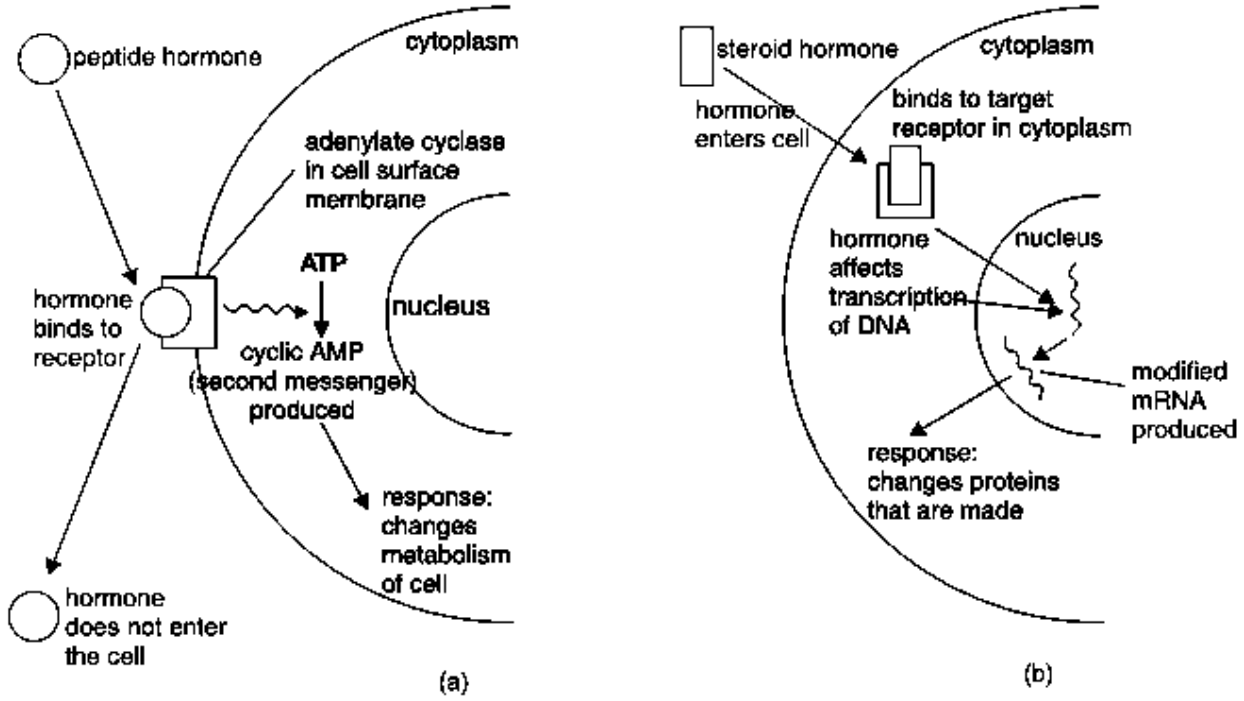


Figure 6. Mechanism of hormone action

PEPTIDE HORMONES

Hormones of the Pancreas

Secretory gland. The pancreas is both an exocrine and endocrine gland. It is situated transversely below and behind the stomach between the curve of duodenum and spleen. It is a compact and lobulated organ. It weighs about half a pound and resembles an elongated cone lying on its side. The broad end or '*head*' of the pancreas is located next to a curve of the duodenum, the part of the small intestine just beyond the stomach.

The gland tapers off to the left in the direction of the spleen and left kidney and ends in a portion called 'tail'. Barring cyclostomes, the pancreas in all the vertebrates is composed of two types of cells:

(*a*) the glandular cells or *acinar* or *acini* (exocrine), which make up the bulk of the pancreatic tissues and secrete digestive juices into the duodenum by the pancreatic duct.

(*b*) the polygonal cells or *islets of Langerhans* or *islet tissue* (endocrine), which do not have any means for emptying their secretions externally but instead pour their secretions (*i.e.*, insulin and glucagon) directly into the blood. Each pancreas has about 1,00,000 islets of Langerhans, which are clusters of various types of cells. These islets in mammals contain 3 major types of cells: α-cells, β-cells and δ-cells. Each islet contains between 1,000 and 2,000 β-**cells,** which were first described in 1869. The β-cells contain granules which are insoluble in alcohol and manufacture a hormone insulin, store it and eventually release it directly into the bloodstream at the appropriate times. These amazing cells (*i.e.*, β-cells) are also capable of measuring the blood glucose level within seconds to within a range of 2 mg %. Using this information, they can determine how much insulin is needed, and, within a minute or so, secrete the precise amount of required insulin. The α-**cells** contain granules which are soluble in alcohol and produce another hormone, glucagon. The α-cells tend to be arranged about the

periphery of the islets. The existence of α-cells is dubious in cyclostomes. Of the two cell types, the α-cells predominate in the reptiles and birds, whereas in amphibians and mammals, the β-cells are more abundant.

Insulin

*Structure***.** Insulin (*insula*L = island) was first isolated in 1922 from the pancreas of dogs by Banting and Best, both of the University of Toronto, Canada. They also demonstrated the curative effect of pancreatic extract in dogs ailing with diabetes mellitus. Abel and his associates (1926) obtained insulin in crystalline form (Fig. 31–27) and also demonstrated its protein nature. *Insulin is, in fact, the first hormone to be recognized as a protein.*

The two polypeptide chains are held together by cross linkages of two disulfide bonds. The acidic chain A contains 21 residues and the peptide chain B having 30 residues. It has a molecular weight of 5,733 and is isoelectric at pH 5.4. Human insulin, however, has a molecular weight of 5,808. Insulin is destroyed by alkali but is relatively stable in acid solutions. Reduction of the disulfide bond results in a loss of biologic activity. Zinc is always found with this hormone but is not a part of the insulin molecule.

*Biosynthesis***.** β-cells of the pancreas synthesize insulin by the ribosomes of the endoplasmic reticulum. Previously, it was suggested that the two chains of insulin are synthesized independently and later these combine by disulfide bonds. But now Donald F. Steiner *et al* (1967) have shown that it is formed from its precursor, *proinsulin*. Proinsulin has been isolated and purified from pancreatic extracts. It is a linear protein with 84 amino acid residues and has a molecular weight of about 9,100.

The transformation of proinsulin to insulin takes place in the granules and not in the endoplasmic reticulum where synthesis of proinsulin takes place. The conversion, which is brought about by lysosomal proteolytic enzymes, consists in cleavage of a 33 amino acid-connecting peptide chain from the proinsulin molecule leaving behind insulin (figure. 7).

$$\text{Proinsulin} \xrightarrow{\text{Proteolytic cleavage}} \text{Insulin} + \text{Peptide}$$

As proinsulin comprises only 5% of the total insulinlike protein of the islets of Langerhans, it is not a storage form of insulin. It rather appears essential in the formation of the disulfide bonds which are indispensable for the biological activity of insulin. The formation of proinsulin has been demonstrated in the pancreatic tissues of bovine, porcine, rat and man as well.

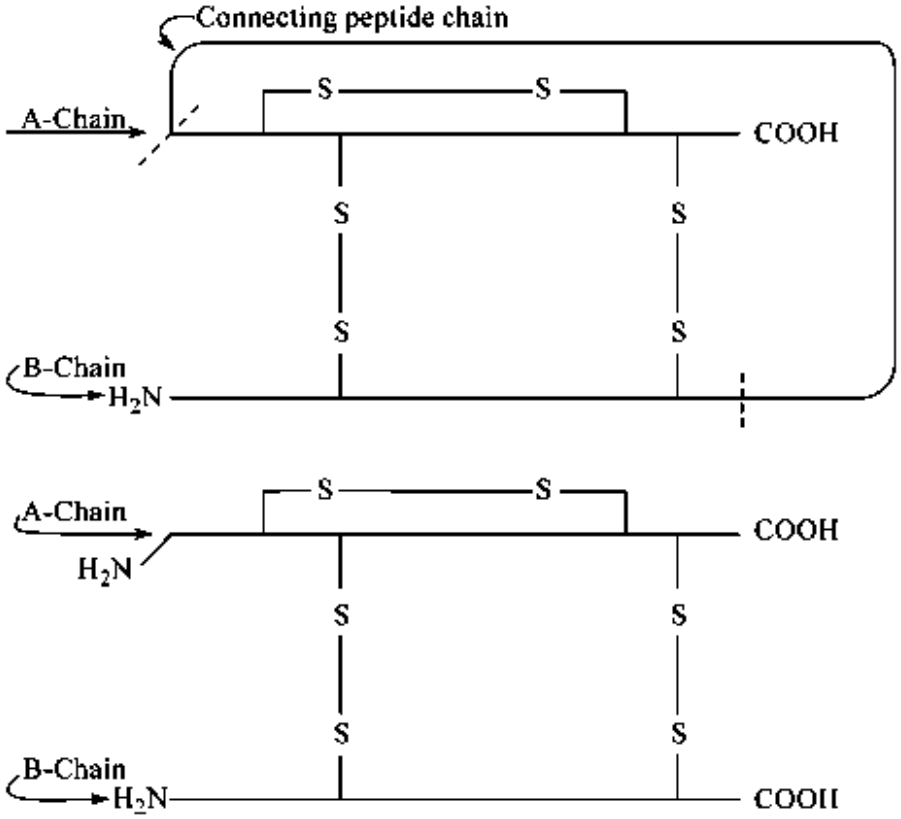


Figure 7. Insuline structure

Functions. Insulin has a profound influence on carbohydrate metabolism. It facilitates entry of glucose and other sugars into the cells, by increasing penetration of cell membranes and augmenting phosphorylation of glucose. This results in lowering the sugar content of the blood – a fact leading to its common name, **hypoglycemic factor**, which may be abbreviated as **hG-factor.** Insulin administration promotes protein synthesis (proteogenesis) by assisting incorporation of amino acids into proteins. This effect is not dependent on glucose

utilization. At the same time, it also acts as an *antiproteolytic agent*, *i.e*., discourages excessive breakdown of tissue protein. This action is similar to that of GH and testosterone. Synthesis of lipids (lipogenesis) is also stimulated by administration of insulin. Insulin also influences the inorganic metabolism *esp*., that of phosphate and potassium. Insulin administration lowers the blood phosphate level and facilitates absorption of inorganic phosphate by the cells. This phosphate appears within the cells as ATP. A similar mechanism operates in potassium uptake.

It may be said, in general, that insulin promotes anabolic processes (synthesis of glycogen, fatty acids and proteins) and inhibits catabolic ones (breakdown of glycogen and fat).

*Insulin deficiency***.** The deficiency of insulin caused either by inadequate insulin production or by accelerated insulin destruction, leads to *diabetes mellitus* in man.

This disease is characterized by:

1. an increase in blood sugar or glucose (hyperglycemia) from a normal value of 80 mg/100 ml of plasma to abnormal value ranging between 150-200 mg/100 ml of plasma.

2. the appearance of sugar in the urine (glycosuria); with the result, the victim’s urine tastes sweet.

3. an increase in concentration of ketone bodies in the blood (ketonemia) and in the urine (ketonuria).

4. the excretion of large quantities of urine (polyuria), frequently at night (nocturia), leading to dehydration.

5. the excessive drinking of water (polydipsia) on account of an unrelenting thirst.

6. the excessive eating (polyphagia) due to feeling constant hunger. This is because the tissues cannot utilize glucose normally, even though they need fuel.

7. the lack of energy (asthenia) which is apparently caused mainly by loss of body protein.

Diabetes mellitus is of 2 types: type I (insulin-dependent) and type II (noninsulin-dependent). The use of Roman numerals probably dignifies the importance of this classification.

Type I (Insulin-dependent diabetes mellitus, IDDM): IDDM occurs because the insulin producing β-cells are destroyed and there is not enough insulin produced. In the past, there was treatment that had some measure of success. This was relative starvation. People with IDDM had very short careers. The former synonyms for this disease are brittle diabetes or juvenile diabetes. Type II Noninsulin-dependent diabetes mellitus, NIDDM) : NIDDM is caused by a relative insulin insufficiency due to insulin resistance– the inability of the insulin to tell the cells to use glucose– plus insufficient insulin to overcome this resistance. Patients with NIDDM often lived for many years, if they heroically reduced their weight to live with the small amount of insulin that might be available. In a sense, this was organised starvation. NIDDM is also known by the former names, stable diabetes or adult-onset diabetes. In case of type II diabetes, it may be said that heredity may load the cannon, but stress or obesity pulls the trigger.

Glucagon

Structure. Glucagon was first isolated in crystalline form by Behrens and others. This peptide hormone has a molecular weight of 3,485 and is isolectric at pH 8. It has 29 amino acid residues (of 15 different types) arranged in a linear row. Histidine is the N-terminal amino acid and threonine, the C-terminal amino acid. Unlike insulin, it contains no cystine, proline or isoleucine, but possesses Parenteral is any route outside the gastrointestinal tract, including subcutaneous, intramuscular, intraperitoneal and intravenous injections or infusions. In practice, parenteral feeding is done intravenously. The small amount of sulfur present is, thus, in the form of methionine rather than cystine.

*Functions***.** Like insulin, glucagon also influences carbohydrate metabolism but in an opposing way. Glucagon (as also the other hormone, epinephrine) activates the enzyme adenyl cyclase which converts ATP to cyclic AMP. The latter compound activates phosphorylase *b* kinase which, in its turn, activates phosphorylase *b* to yield phosphorylase *a*. This releases glucose-lphosphate from glycogen of liver. Glucose-l-phosphate then yields free glucose in blood, whereby increasing blood sugar contents (figure 8). It is because of this reason that the hormone is also termed as **hyperglycemic factor** or **HG-factor**.

In contrast to epinephrine, glucagon does not cause an increase in blood pressure. Therefore, glucagon and not epinephrine has found clinical applications and is administered in patients with acute hypoglycemia.

Acting in the liver, it stimulates glycogenolysis (glycogen breakdown) and gluconeogenesis (production of glucose from noncarbohydrate sources such as proteins and fats). The former function is similar to that of ACTH and epinephrine.

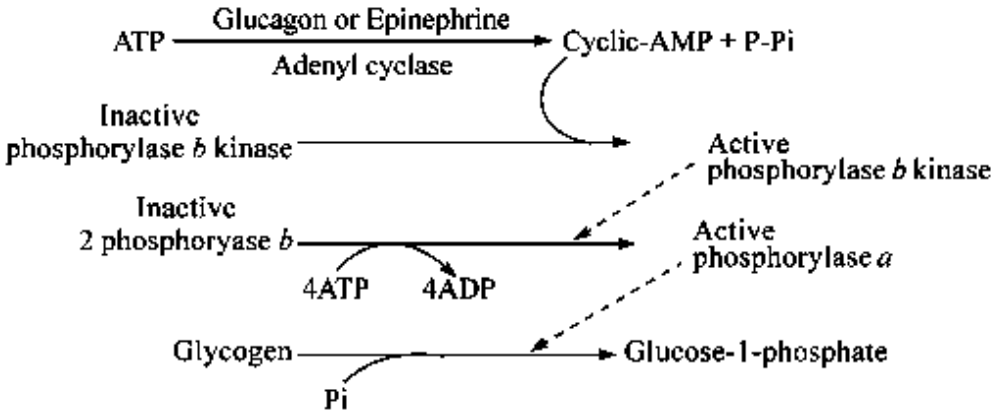


Figure 8. Glucagon action

Glucagon also affects lipid metabolism by accelerating ketogenesis and inhibiting synthesis of fatty acids. Glucagon has a catabolic action on proteins. Its administration in the body results in excretion of enough nitrogen and phosphorus, in decrease of liver tissues and in loss of body weight.

Hormones of the Hypophysis or Pituitary Gland

*Secretory gland***.** Hypophysis (meaning undergrowth) is so named because of its location below the brain as an undergrowth. Its synonym pituitary gland is, however, misleading as the gland is not concerned with the secretion of mucus or phlegm (*pituita*L = phlegm), as was thought previously. This is an unpaired small ovoid gland and is no larger than the end of the little finger. It is located at the base of the brain and lies below the diencephalon in a depression of basis phenoid bone of the skull called sella turcica. It is a complex structure formed of ectodermal outgrowth of the mouth cavity and down growth of the infundibulum. The human hypophysis is a reddish- grey oval structure and measures about 10 mm in diameter.

Its average weight varies in the two sexes: 0.5-0.6 g in males and 0.6-0.7 g in females. It consists of 3 lobes:

(*a*) an anterior richly vascular largest lobe, pars distalis or adenohypophysis.

(*b*) an intermediate relatively avascular smallest lobe, pars intermedia.

(*c*) a posterior neural lobe, pars nervosa or neurohypophysis.

While all the three parts are important, it is the anterior lobe that seems to be essential to life. This gland plays perhaps the most dominant role as it secretes hormones which govern the secretion of other endocrine glands (like thyroid, adrenal and gonads) and also its secretions have a direct effect on the metabolism of nonendocrine tissues. It has, therefore, aptly been described as the '*master gland*' of the system or the 'master (= *conductor*) *of endocrine orchestra*'. However, the view held by some biochemists is that since the hypophysis is subservient to the nervous system and some of the other endocrine glands, it is erroneous to call this gland as the master gland of the body.

Pars distalis or Adenohypophysis. The anterior lobe is the largest and shares about 70% of the total weight of hypophysis. The adenohypophysis originates from an embryonic invagination of the pharyngeal epithelium called Rathke's pouch. This explains the epithelioid nature of its cells. It consists of glandular epithelial

cells of varying shapes and sizes, arranged in columns separated by sinusoids containing blood. In general, there is one type of cell for each type of hormone that is produced in this gland. These various cell types can be differentiated from one another on the basis of special staining techniques (the only likely exception to this is that the same cell type may secrete both luteinizing hormone and follicle-stimulating hormone). Using acid-base histological stains, only 3 types of cells may be differentiated in this region:

(*a*) *acidophils or* α *cells* – these stain strongly with acidic dyes (acid fuchsin) and secrete growth hormone and prolactin.

(*b*) *basophils or* β *cells*– these stain strongly with basic dyes (aniline blue) and secrete luteinizing hormone, follicle-stimulating hormone and thyroid-stimulating hormone.

(*c*) *neutrophils or chromophobe cells* – these do not stain with either and are believed to secrete adrenocorticotropic hormone.

The anterior lobe produces hormones which govern the production of hormones secreted by other glands. These hormones are called as **tropins** (*tropos*G = turning) or **trophic** (*trophikos*G = nursing) **hormones**. Evidences available indicate that the rate of secretion of a trophic hormone is inversely proportional to the concentration, in the blood, of the hormone with which it is related. For example, a high blood level of thyroid hormone tends to inhibit the secretion of TSH from the adenohypophysis and a low level causes an increased production of it.

Neurohormones – The secretion of thyrotropin (as of almost all other pituitary hormones) is controlled by the hormones (or factors) released from hypothalamus, a region of the brain immediately proximal to the pituitary. These hormones are called as **hypothalamo-releasing hormones** or **hypothalamic factors.** These have been classified as *neurohormones*, *i.e.*, those produced by the nerve cells. These are unlike *neurohumors* (*e.g.*, acetylcholine, serotonin, norepinephrine etc) which are released at nerve endings and activate the adjacent

nerve bodies. The neurohormones, on the contrary, are released into the blood and activate cells a little far from their point of release. These are introduced into the capillary of the hypothalamo-hypophyseal portal system at the floor of the hypothalamus called median eminence. In addition, the release of anterior pituitary hormone may be inhibited by *a release inhibiting* factor which passes down the same hypothalamo-hypophyseal portal veins.

The various hypothalamic factors controlling the release of pituitary hormones have been listed in Table 1.

Table 1

Hypothalamic factors controlling the release of pituitary hormones

S.N.	*Pituitary Hormones*	*Hypothalamic Releasing Factors**
1.	Thyrotropin, TSH	Thyrotropin-releasing factor, TRF
2.	Corticotropin, ACTH	Corticotropin-releasing factor, CRF
3.	Follicle-stimulating hormone, FSH	Follicle-stimulating hormone-releasing factor, FSH-RF
4.	Luteinizing hormone, LH	Luteinizing hormone-releasing factor, LH-RF
5	Prolactin, PL	Prolactin-releasing factor, PRF
6.	Growth hormone, GH	Growth hormone-releasing factor, GH-RF
7.	Melanocyte-stimulating hormone, MSH	Melanocyte-stimulating hormone-releasing factor, MRF

Some 30 tropins are secreted from the anterior lobe. The four important tropins are described below.

1. Thyrotropin or thyroid-stimulating hormone, TSH. It is a glycoprotein with molecular weight about 30,000. Each molecule has 8-9 cystine residues and the disulfide groups are present as intrachain linkages rather than interchain linkages.

In general, it stimulates the activity of thyroid gland and enhances the rate of certain reactions such as:

(*a*) removal of iodide from blood by thyroid

(*b*) conversion of iodide to thyroid hormones

(*c*) release of hormonal iodine from thyroid.

The release of thyrotropin is controlled by another hormone from hypothalamus called thyrotropinreleasing factor, TRF.

2. Corticotropin or adrenocorticotrophic hormone, ACTH. Corticotropin is a straight chain polypeptide with a molecular weight of about 4,500 and consists of 39 amino acid residues in mammals like man, ox, sheep and pig. The most potent segment of activity is from residue 15 to 18. ATCH molecule in these species differs from each other only in the constituents present from residue 25 to 33. Thus far, no differences in residues 1-24 and 34-39 have been reported.

ATCH, in general, has a stimulatory effect on the hormone-producing capacity of the adrenal cortex. ATCH administration leads to accelerated gluconeogenesis with accompanied retardation of protein synthesis in all tissues except liver. It also possesses an intrinsic melanocyte-stimulating activity, causing darkening of the skin in a manner similar to that of another hormone, MSH. Over secretion of ACTH results in Cushing's disease, already described earlier. Certain peptides found in hypothalamus and also in neurohypophysis have ACTH-releasing activity. These have been termed as corticotropin-releasing factor, CRF.

3. Gonadotropins or gonadotrophic hormones, GTH. These hormones control the development and functioning of the gonads which remain dormant until the age of 12-14 years in the human beings.

Damage to certain areas of the hypothalamus greatly decreases the secretion of gonadotrophic hormones by the anterior pituitary. If this occurs prior to puberty, it causes typical eunuchism. The damage often causes simultaneous overeating because of its effect on the feeding centre of the hypothalamus.

Consequently, the person develops severe obesity along with the eunuchism. This condition is called **adiposogenital syndrome** or **Frohlich's syndrome** or **hypothalamic eunuchism**. Three gonadotropins are known.

A. Follitropin or follicle-stimulating hormone, FSH. It is a glycoprotein that contains galactose, mannose, galactosamine, glucosamine, sialic acid, fucose and uronic acid. It has a molecular weight of about 30,000 in man. In human

females, it induces the growth of graafian follicles resulting in an increased weight of the ovary. In males, however, FSH promotes spermatogenesis by stimulating the development of seminiferous tubules, thus leading to the formation of a large number of spermatocytes. The release of this hormone is controlled by another hormone from hypothalamus called folliclestimulating hormone-releasing factor, FSH-RF.

B. Luteinizing hormone, LH or interstitial cell-stimulating hormone, ICSH. It is a peptide hormone with molecular weight of about 26,000 (in man) or 100,000 (in swine). It lacks tryptophan but has a high content of cystine and proline. Each molecule contains 10 glucosamine and 3 galactosamine residues. In females, LH is concerned with the ripening and rupturing of ovarian follicles, which later transform into corpus lutea. It also induces the development of interstitial cells of both the ovaries and the testes a fact responsible for its nomenclature.

The secretion of LH is controlled by luteinizing hormone-releasing factor, LH-RF, a secretion from hypothalamus. The long-acting analogue of LH-RF has been found useful in the treatment of precocious puberty in females by Florence Comite et al (1983), the American researchers at the National Institute of Health. Puberty is initiated by pulsed nocturnal secretions of gonadotropins that result from the release of the hormone LH-RF by the hypothalamus gland in the brain. The administration of LH-RF analogue "initially stimulated but subsequently inhibited" the release of LH and FSH, the two sex hormones that initiate puberty.

C. Luteotropin or luteotrophic hormone, LTH. Because of its broad spectrum of effects on vertebrates in general, *luteotropin is the most versatile of all the adenohypophyseal hormones.* It is also the first anterior pituitary hormone to be obtained in pure form. This is also a peptide hormone with 198 amino acid residues and a molecular weight of about 23,500. It has 3 disulfide bonds between cysteine residues at 4-11, 58-173 and 190-198 (Li *et al*, 1971). It differs from FSH and LH in that it contains no carbohydrate. It is thermolabile and is destroyed by tryptic

digestion. In pure form, it has no growthpromoting, thyrotropic, diabetogenic, adrenotropic or gonadotropic activities. However, in association with estrogen, luteotropin promotes the growth of the mammary glands (mammogenesis) and also induces secretion of milk (lactation) at the time of child birth (parturition). Henceforth, this hormone is variously called as *prolactin*, PL or *lactogenic hormone or mammotrophic hormone*, MH. It also stimulates glucose uptake and lipogenesis. Along with androgens, it causes the development of secondary male sex characters. In rat, at least, prolactin also has gonadotrophic activities in that it maintains functional corpora lutea in hypophysecto-mized animals. It also acts as an anabolic agent mimicking the effects of growth hormone.

In fact, prolactin is credited with performing some more than 80 functions and it is for the same reason that it has been jocularly termed as a "*jack-of-all-trades*." According to Nicoll and Bern (1971), these various functions of prolactin fall under 5 major categories : reproduction, osmoregulation, growth, integument and synergistic effect with the steroid hormones.

4. Somatotropin or somatotrophic hormone, STH or growth hormone, GH.

Somatotropin obtained from human hypophysis is a protein with molecular weight 27,000 (41,600 in pig) and an isoelectric point 4.9. It has 190 amino acids and consists of 2 disulfide bridges between adjacent cysteine residues at 53-164 and 181-188. The N-terminaland C-terminal residues are both phenylalanine. Unlike other adenohypophyseal hormones, the various effects of somatotropin are not due to its influence on other endocrine glands. It acts rather directly upon various tissues to produce diverse effects. *It is, therefore, not a true tropic hormone*. The various metabolic activities particularly attributed to this hormone are listed below.

(*a*) It affects the rate of skeletal growth and gain in body weight. In adult animals with closed epiphyses, SH stimulates chondrogenesis followed by ossification.

(*b*) It causes abnormal increase in blood sugar by producing degenerative changes in islets of Langerhans (*diabetogenic effect*).

(*c*) It stimulates the growth of the islets of Langerhans (*pancreatotropic effect*).

(*d*) It controls the production of fat in the body and its deposition in the liver (*ketogenic effect*).

(*e*) It prevents the fall of muscle glycogen in fasting and hypophysectomized animals.

(*f*) It also stimulates milk secretion in cows and also the growth of mammary glands in hypophysectomized rats (*galactopoietic effect*).

(*g*) STH is also known to cause adrenal enlargement (*corticotropic effect*).

The adrenal enlargement can be greatly augmented by simultaneous treatment with low doses of thyroxine, thus indicating the participation of thyroid gland along with the hypophysis in this action. It is now recognized that as people live to their 70s and beyond, the effect of declining hormones may contribute significantly to chronic, debilitating and costly illnesses. Among the well-known **attributes of ageing** that hormone loss may bring about are loss of muscle mass and strength, an increase of body fat, particularly fat around the abdomen, a weakening of the bones, a decline in immune responses and a general loss of energy. In 1990s, attention has now been diverted to the study of growth hormone and other trophic hormones, substances that promote growth or maintenance of tissues. They may, at least, have a promise for halting or reversing degenerative changes in bones, muscles, nerves and cartilage.

Pituitary diabetes – A general increase in the secretion of all the adenohypophyseal hormones causes elevated blood glucose concentration. This condition is clinically designated as pituitary diabetes. It, however, differs from diabetes mellitus, which results from insulin deficiency, in the following respects:

I. In pituitary diabetes the rate of glucose utilization by the cells is only moderately depressed whereas in diabetes mellitus almost no utilization of glucose takes place.

II. Many of the side effects that result from reduced carbohydrate metabolism in diabetes mellitus are, however, lacking in pituitary diabetes.

Pars Nervosa or Neurohypophysis. The neurohypophysis develops from an outgrowth of the hypothalamus. This explains the presence of glial type cells in the gland. The posterior pituitary secretes 2 hormones: ocytocin and vasopressin.

These were separated by Kamm and others.

1. Ocytocin (*ocy*G = quick ; tokosG = birth) or **pitocin.** It is a nonapeptide amide. A disulfide bond is present to link the two cysteine residues present in the molecule (figure 9). Ocytocin preparations from man, cow and pig are identical. Besides mammals, it is also found in chondrichthyes, lung fishes, amphibians and aves. Ocytocin stimulates the contraction of smooth muscles, *esp*., those of uterus, thus facilitating childbirth. Commercial form of ocytocin is frequently used to induce 'labour'. In general, it also causes contraction of other smooth muscles like those of intestine, urinary bladder and the ducts of mammary glands resulting in milk ejection. It is, therefore, also called as *milk-let-down-ejection factor*. Ocytocin levels are increased by suckling which is necessary for the continued formation of milk by the breasts. Optimum milk secretion lasts for about 8 to 10 months after which it gradually falls and ultimately ceases.

2. Vasopressin or **pitressin.** It is also a cyclic nonapeptide amide and resembles ocytocin except that isoleucine is replaced by phenylalanine and leucine by arginine (figure. 9). The hormone was synthesized, in 1953, by V. du Vigneaud and colleagues from U.S.A. and du Vigneaud received the Nobel Prize in 1955 for the first synthesis of a polypeptide hormone.

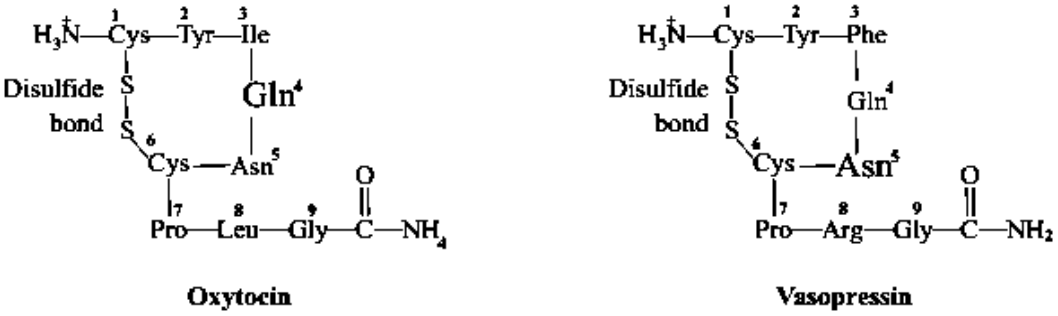


Figure 9. Oxytocin and Vasopressin structure

Vasopressin (VP), obtained from pig, differs from that of human beings (shown above) in arginine being replaced by lysine at position 8. It is, therefore, better called as *lysine vasopressin and that* from human beings as *vasopressin.*

Vasopressin regulates many functions:

I. Circulatory or pressor action. Vasopressin causes a rise in blood pressure by contraction **Ocytocin** is often called oxytocin. However, the name ocytocin is preferred since its Greek origin (meaning quick birth) tallies with it and also it avoids confusion with the prefix oxy = oxygencontaining, as the hormone refers in no way to oxygen.

The term ‘insipidus’ (= tasteless) dates from the time when the only method of testing urine was to taste it after diluting, and in this condition the urine is tasteless of peripheral blood vessels. It is, thus, a vasopressor substance and for this reason it is termed ‘vasopressin’. It has been used in surgical shock as an adjuvant in elevating blood pressure. It may also be used at the time of delivery to overcome uterine inertia. The effect is similar to that caused by adrenalin. However, the rise in blood pressure caused by vasopressin lasts much longer than that caused by adrenalin which wears off in a few minutes.

II. Antidiuretic action. It brings about a reduction in the urine volume by causing renal tubules to withhold more water. Consequently, the urine passed is rich in sodium chloride, phosphate and total nitrogen. It was earlier thought that this antidiuretic effect was due to a different hormone called *antidiuretic hormone*,

ADH. But it is now established that the two hormones (vasopressin and ADH) are one and the same. Vasopressin, therefore, finds use against persons suffering from **diabetes insipidus**, a disease characterized by excretion of large quantities of urine (polyuria) and a marked thirst (polydipsia). The urine specific gravity remains almost constant between 1.002 and 1.006. The urine output becomes 4 to 6 litres a day but can be sometimes as high as 12 to 15 litres a day, depending mainly on the amount of water taken by the patient. Furthermore, the rapid loss of fluid in the urine creates a constant thirst which keeps the water flushing throughout the body. The patient, thus, has a tendency to become dehydrated. But this tendency is quite well offset by the increased thirst. The disease may be controlled by administration of posterior pituitary extracts subcutaneously or even by nasal instillation.

Hypopituitarism. Insufficient secretion of pituitary hormones (or hypopituitarism) may occur as a result of pituitary tumours or atrophy of the gonad. Hypoactivity of this gland may lead to the following disorders:

1. **Dwarfism.** It refers to the arrested growth of the individuals. It is of 2 types:

(*a*) Lorain type – short statured individuals with a head large in comparison to the rest of the body; usually intelligent but unattractive.

(*b*) Fröhlich type – obesity and arrested sexual development; men-tally below normal and usually lethargic.

2. **Panhypopituitarism.** It is caused because of the destruction of the gland, thus leading to cessation of all hypophyseal functions.

3. **Pituitary myxedema.** It is caused due to the lack of TSH and produces symptoms similar to those described for primary hypothyroidism.

Hyperpituitarism. It refers to the overproduction of hypophyseal hormones. Hypersecretion of this gland leads to **gigantism** during childhood or adolescence, *i.e.*, before closure of the epiphyses. The disease is characterized by overgrowth of the bones, especially at joints, leading to a tall individual with 2 to 2.5 M height. The limbs usually become disproportionately large. In human adults with closed

epiphyses, excessive secretion of pituitary hormones causes **acromegaly** (*acron*G = extremity). The chief symptoms of this disease are:

1. consistent overgrowth of the bones of face, hands and feet (*acral* parts; hence the term acromegaly) so that the patient often complains of having have to change globes and shoes frequently as they no longer fit.

2. protrusion of the lower jaw (prognathism). Overgrowth of the malar, frontal, and basal bones combines with prognathism to produce the coarse facial features called *acromegalic facies.*

3. bowing of the spine (kyphosis)

4. overgrowth of the body hair

5. thickening of the soft tissues of nose, lips and forehead

6. enlargement of the visceral organs such as lungs, heart, liver and spleen

7. increased sexual activity in the beginning which is ultimately followed by atrophy of the gonads. This leads to impotence in man and amenorrhea in woman. A classical example of acromegaly is that of Akhenaton, the Pharaoh who ruled Egypt in the years 1379–1362 BC. His predominant facial features strongly suggest that he suffered from acromegaly. Acromegalic persons usually have enlarged facial & chiral features.

Hypophysectomy. The effects of hypophysectomy (removal of hypophysis) appear to be almost entirely due to the loss of adenohypophysis. Removal of only the neurohypophysis exerts no striking dysfunctions. Hypophysectomy, in general, leads to:

1. gonadal atrophy in either sex

2. atrophy of the thyroid

3. atrophy of the adrenal cortex

4. loss of body tissue with some reversion to younger characters, *i.e.*, appearance of juvenile hair.

Hormone of the Parathyroid Secretory gland.

The parathyroids were first discovered by Sandström in 1880. In the human beings, there are usually four small parathyroid glands so closely associated with the thyroid gland that they remained undiscovered for some time. Each parathyroid gland is a reddish or brownish, oval body, measuring about 5-7 mm in length, 3-5 mm in width and 1-2 mm in thickness. The four glands together weigh only 0.1 to 0.2 gm. The glands have a macroscopic appearance of dark brown fat, therefore these are difficult to locate and hence often removed during thyroidectomy (removal of the thyroid). Of the four parathyroids, two lie embedded in the thyroid and are called as *internal parathyroids* ; the other two lie close and behind the thyroid and are known as *external parathyroids.* There may be fewer than four or as many as eight parathyroids. The extra ones are scattered along the trachea and are called as accessory parathyroids. Occasionally, the parathyroids are located in the anterior mediastinum or, rarely, in the posterior mediastinum. The parathyroids are, however, lacking in the fishes.

Histologically, the parathyroid of the adult human being consists mainly of chief cells (= principal cells) and oxyphil cells. The oxyphil cells are usually absent in young human beings. The chief cells are concerned with the secretion of the parathyroid hormone. The oxyphil cells are rich in mitochondria but lack glycogen. Their function is uncertain. They are regarded as probably aged chief cells that still secrete some hormones.

Structure. Parathyroids secrete a hormone called parathyroid hormone (parathormone, PTH) or **Collip's hormone.** PTH has been isolated in pure form. It is a linear polypeptide consisting of 84 amino acid residues and has a molecular weight of about 7,000 to 8,500. Potts and others (1971) have, however, indicated that the physiologic activity of this hormone on both skeletal and renal tissues is contained within the first 34 amino acids from the N-terminal of the chain. As is also true for many other hormones (such as α-MSH and corticotropin), the PTH

can be cleaved to form smaller but still active units. Oxidation inactivates the parathormone rapidly.

Functions. The principal sites of parathyroid action are bones, kidney and gastrointestinal tract. Following physiological functions are attributed to this hormone:

1. *Bone resorption* – It exerts a direct influence on the metabolism of bone, leading to an increased release of bone Ca^{2+} into the blood. The exact mechanism behind this phenomenon is not truly known. It has, however, been suggested that the hormone stimulates the production of citric acid in the bone tissues and an increased concentration of citrate ions leads to the removal of phosphate from calcium phosphate, the bone material. The bone is, thus, made soluble.

2. *Renal reabsorption of calcium* – In the kidney, parathormone affects renal tubular reabsorption of calcium and reabsorption or secretion of phosphate. It increases the elimination of calcium and phosphorus in the urine. It is interesting to note that the secretion of this hormone is controlled by Ca^{2+} ion concentration of the blood itself. As the Ca^{2+} ion concentration increases, PTH secretion decreases tending to preserve the original condition. This affords an excellent example of feedback mechanism of metabolic control.

3. *Increase in osteoelastic activity* – Parathormone increases osteoelastic activity with augmented growth of the connective tissue.

4. *Calcium homeostasis* – An optimum Ca^{2+} concentration is necessary for various functions of the body, *viz*., normal transmission of impulses, the contraction of the muscles, the formation of the bones, the coagulation of the blood etc.

The three hormones of importance in this process of calcium homeostasis, as it is called, are vitamin D, PTH and calcitonin. The vitamin D can be classified as a hormone since it is manufactured in the skin (which is an organ) which it is exposed to light. An interesting finding is the observation that in the presence of

vitamin D, the parathormone sitmulates the release of calcium accumulated by mitochondria.

Hypoparathyroidism. Undersecretion of PTH causes a decrease in Ca contents of the blood from the normal 10 mg per 100 ml to 7 mg per 100 ml (hypocalcemia) which leads to excessive contraction of the muscles (convulsions). In fact, convulsions occur when the calcium is further decreased to 4 mg per 100 ml of plasma. As the calcium decreases in the blood, there is a decrease in the urine.

However, during this period, the phosphorus in plasma increases from a normal 5 mg per 100 ml to 9 mg per 100 ml and even higher (hyperphosphotemia). These changes develop into a fatal disease called **muscular twitchings** or **tetany**. It is characterized by locking up of the jaw, rapid breathing, increased heart beat, rise in temperature and ultimately death due to asphyxia. The signs of tetany in man include **Chvostek's sign**, a quick contraction of the ipsilateral facial muscles elicited by tapping over the facial nerve at the angle of the jaw; and **Trousseau's sign**, a spasm of the muscles of the upper extremity that causes flexion of the wrist and thumb with extension of the fingers. Tetany can be relieved either by the administration of a soluble calcium salt or of PTH.

Hyperparathyroidism. An increase in PTH production is usually due to a tumour of the gland (parathyroid adenoma). Oversecretion of PTH in man results in a cystic bone disease variously called as **osteitis fibrosa cystica** or **von Recklinghausen's disease** or **neurofibromatosis.** It is an autosomal dominant condition. The disease is characterized by increased calcium contents of the blood (hypercalcemia) usually up to 20 mg calcium per 100 ml palsma, decreased phosphate concentration and increased renal excretion of calcium. Overproduction of parathormone causes calcium and phosphorus to move out of the bones and teeth, making them soft and fragile. Such patients, therefore, suffer fractures of the bones very frequently. Cysts in the bones are another characteristic of this disease.

AMINO ACID DERIVATIVES

Thyroidal Hormones Secretory gland.

The thyroid is the largest endocrine gland in the body. It was first described by Whartonin in 1659 who gave it the descriptive |name, thyroid because of its resemblance to a shield (*thyreoides*G = shield-shaped). In man, the gland consists of two lobes on either side of and anterior to the trachea just below the larynx. The two lobes are connected across the ventral surface of the trachea with a narrow bridge called isthmus, making the entire gland more or less H-shaped in appearance. The isthmus crosses infront of the 2nd, 3rd and 4th tracheal ring. In the adult, the gland weighs about 25 to 30 gm. The thyroid gland receives blood flow about 5 times its own weight per minute. It has a blood supply as rich as that of any other area of the body barring probably the adrenal cortex. The thyroid is presumed to be homologous with the endostyle of the early vertebrates.

Histologically, the thyroid gland is composed of a large number of tiny closed vesicles called *follicles,* 150 to 300 microns in diameter. The follicles are held together by areolar tissue and are surrounded by a rich network of capillaries. Each follicle is lined with a single peripheral layer of columnar or cuboidal *epithelioid cells* that secrete into the interior of the cells. Its lumen is filled with a secretory substance called colloid. The major constituent of colloid is a large protein called thyroglobulin, which contains the thyroid hormones. Once the secretion has entered the follicles, it must be absorbed back through the follicular epithelium into the blood before it can perform its function in the body. The thyroid gland is, thus, unique amongst the endocrine glands in that *it stores its hormone as a colloid in small vesicles in the gland*. The other endocrine glands, however, store their hormones in the cells themselves. As age advances, the thyroid activity tapers off. That’s why elderly persons feel colder, since their body does not produce sufficient heat.

Structure. Thyroid contains large amounts of elemental iodine which is bound to a protein named iodothyroglobulin or simply thyroglobulin. It is a glycoprotein with a molecular weight of about 650,000 and iodine content from 0.5 to 1.0%. This protein represents the storage form of the hormone in the gland.

Evidences available at present indicate that thyroglobulin is hydrolyzed, in the presence of thyrotropin, to release thyroxine (= 3, 5, 3′,5′-tetraiodothyronine) in the blood (figure 10). The release of thyrotropin is, in turn, controlled by the level of thyroxine in the blood.

Thyroxine is one of the earliest recognized hormones. It was so named and isolated first by Kendell in 1915. Harington and Barger (1925) established its chemical formula. It is an iodinecontaining aromatic amino acid and closely resembles tyrosine in structure. Diiodotyrosine is believed to be the precursor of thyroxine.

Besides thyroxine, 3,5,3′-triodothyronine is also produced from enzymatic hydrolysis of thyroglobulin. It is 5 to 10 times more potent in biologic activity than thyroxine. This may, possibly, be due to the fact that triodothyronine is bound loosely by serum proteins and hence diffuses much more rapidly into the tissues. It is present in the blood in much smaller quantities and persists for a much shorter time than does thyroxine. The structure of triiodothyronine and tetraiodothyronine is given in figure 10.

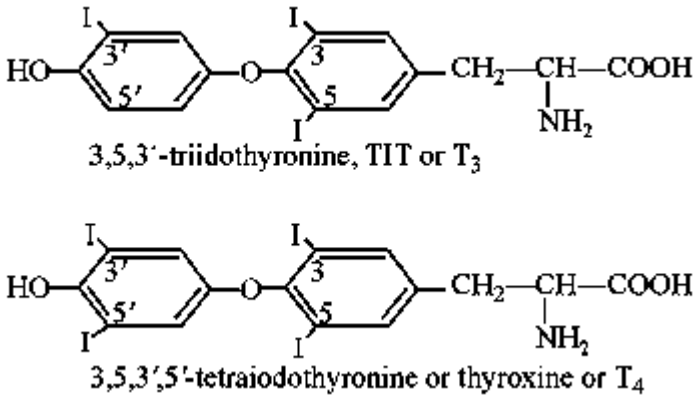


Figure 10. The structure of triiodothyronine and tetraiodothyronine

Functions. Thyroid hormones have widespread effects on the ossification of cartilage, the growth of teeth, the contours of the face and the proportions of the body. They also carry out following functions:

1. They bring about deamination reactions in the liver.

2. They also carry on deiodination in the extrahepatic tissues.

3. These influence oxidative phosphorylation by altering the permeability of the mitochondrial membrane.

4. Their presence accelerates metamorphosis in amphibians. This is so a sensitive test that tadpole has been widely used for the assay of the potency of these hormones.

5. These may increase the level of cytochrome *c* in the tissues. It is, thus, apparent that these hormones affect the general metabolism, regardless of the nature of its specific activity. It is for this reason that the thyroid gland has rightly been called as the '*pace setter*' of the endocrine system.

Thyroid inhibitors or goitrogens. Certain substances act as antithyroid agents by inhibiting the production of thyroxine. This is explained by the fact that these compounds prevent the oxidation of iodide, which means that the iodine cannot be used for the synthesis of thyroxine. Some important thyroid inhibitors are 6-propyl-2-thiouracil, 2-thiouracil, thiourea and the sulfonamides. Thiouracil itself is relatively toxic ; less so are propylthiouracil and thiourea. Of these, propylthiouracil has been used most extensively. It is 3 to 5 times more active than thiouracil. The antithyroid drugs or the goitrogens, as they are also called, are also found in common foods such as cabbage, turnips, spinach, peas etc

Hypothyroidism. Underactivity of the thyroid may result from two causes: a degeneration of thyroid cells or a lack of sufficient iodide in the diet. The disease that results from thyroid cell degeneration is cretinism in children and myxedema in adults.

Cretinism (=feeble-mindedness) is characterized by dwarfism and mental suppression. The cretinic children have infantile features. They possess a large

head and an apathetic face ; their teeth erupt late and the speech is retarded. Early treatment with thyroid-active compounds partially prevents this disease.

Myxedema is characterized by an abnormally low basal metabolic rate (BMR). In it, the adults become mentally lethargic and possess thick puffy skin (edema) and dry hair. The patient shows bagginess under the eyes and swelling of the face. The hair thin on the eyebrows and scalp. As there is deposition of semi-fluid material under the skin, the name myxedema (*myxa*G = mucus; *oidema*G = swelling) is given to this condition. Myxedema also responds well to administration of thyroid-active compounds.

Myxedema is less severe than cretinism. Lack of sufficient iodide in the diet results in thyroid gland enlargement, known as **simple goiter.** It is also associated with a low BMR. This type of goiter is also known as **endemic goiter**, since it is prevalent in areas where the soil and drinking water lack iodide. Simple goiter was once fairly common in some mountainous parts of Switzerland and the United States, where soil and water are deficient in iodine compounds.

Hyperthyroidism or **Thyrotoxicosis.** Abnormally high activity of this gland may occur due to either oversecretion of the gland or an increase in size of the gland. Swelling of the gland results in an **exophthalmic goiter**, characterized by protrusion of the eye balls. In it, the BMR increases considerably above the normal figures ; 80% above normal is not unusual. Consequently, appetite is increased in hyperthyroid individuals. In spite of this, they lose weight and often feel hot because of the increased heat production. Hyperthyroid individuals are, in general, characterized by an above-normal rate of many physiological activities. The clinical syndrome is generally termed **Graves' disease**, after its discoverer Robert James Graves. **Basedow's disease** and **thyrotoxic exophthalmos** are other names of this disease. Not surprisingly, people with hyperactive thyroids (*i.e.*, with Graves' disease), thus, show many symptoms opposite those in hypothyroidism. Hyperthyroidism can be cured by surgical removal of the thyroid (thyroidectomy), treatment with x-rays, injection of radioactive iodide (131I) or by treating with

antithyroid drugs or with agents like thiocyanate or perchlorate which compete with iodide for the uptake mechanism. Propylthiouracil is being particularly used against the Graves' disease.

Thyrocalcitonin or Calcitonin

A quite different type of hormone which has effects of decreasing calcium ion concentration in the blood has been discovered by Copp et al in 1961 as an impurity in the commercial parathyroid extracts. They termed this hypocalcemic factor as calcitonin (CT). *Later researches revealed that this factor originated in the thyroid, rather than in the parathyroids.* This substance was, henceforth, also named as thyrocalcitonin (TCT). It is secreted by the parafollicular cells or C-cells in the interstitial tissue between the follicles of the human thyroid gland. Later, it was discovered that CT is secreted by the ultimobranchial glands of fishes, amphibians, reptiles and birds. In mammals, however, these glands do not exist as such but have become incorporated into either the parathyroids or the thyroid.

The parafollicular cells of human thyroid glands are remnants of the ultimobranchial glands of lower animals. Thyrocalcitonin is a large, unbranched polypeptide containing 32 amino acids and has a molecular weight of about 3,600. It is unique in having no isoleucine and lysine residues. Its amino acid sequence has been determined by Foster in 1968. Thyrocalcitonin acts by causing a transfer of calcium from blood into bone either by increasing calcification of the bones or by diminishing decalcification or by both processes. In other words, itrapidly inhibits calcium withdrawal from bones. This characteristic property, however, promises it to be a therapeutic agent for the treatment of certain types of bone diseases. This action of thyrocalcitonin is counterbalanced by the hypercalcemic hormone, the parathormone which is secreted by the parathyroids.

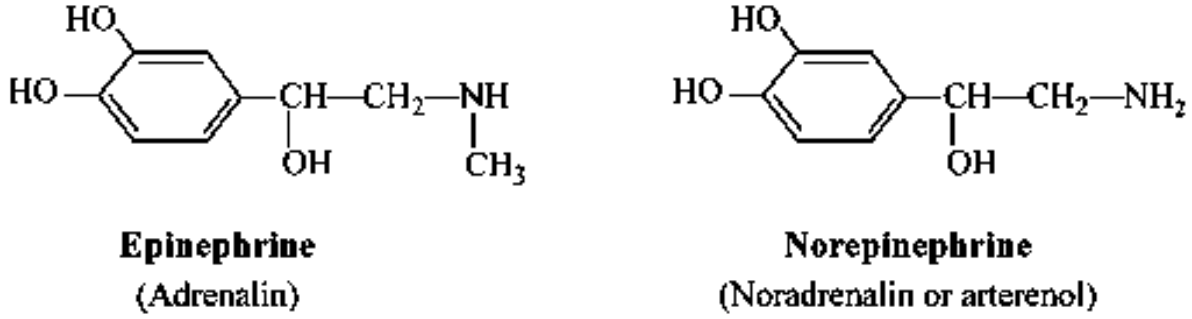
Effect of thyroid hormones on the gonads: For the normal sexual activity to occur, the secretion of thyroidal hormones needs to be almost normal – neither too little nor too more. In the male, deficiency of the thyroid hormones may cause complete loss of libido whereas their hypersecretion, on the contrary, leads to

impotence. Similarly, in the female also, the lack of thyroid hormones leads to greatly diminished libido and often results in menstrual bleeding which may be excessive (menorrhagia) and frequent (polymenorrhea). A hyperthyroid female exhibits greatly reduced bleeding (oligomenorrhea) and sometimes, amenorrhea.

Adrenal Medullary Hormones

As already stated, the adrenal medulla forms the central core of adrenal gland and originates from the neural canal. It is composed of densely packed polyhedral cells containing chromaffin granules. It is highly vascular and receives 6-7 ml of blood per gram of tissue per minute. The chromaffin granules store large quantities of adrenal medullary hormones.

Structure. Adrenal medulla, whose secretion is under nervous control, produces two hormones (figure 11): (*a*) epinephrine or adrenalin ($C_9H_{13}O_3N$) and (*b*) norepinephrine or noradrenalin ($C_8H_{11}O_3N$).



Epinephrine
(Adrenalin)

Norepinephrine
(Noradrenalin or arterenol)

Figure 11. Structures of Epinephrine and Norepinephrine

Epinephrine was the first hormone to be isolated in the crystalline form. The isolation was, however, done by Abel. It has been produced synthetically by Stoltz. Chemically, these two hormones are catecholamines (= dihydroxy-phenylamines) and are closely related to tyrosine and phenylalanine. Norepinephrine, however, differs from epinephrine structurally in having a hydrogen atom in place of the methyl group. The commonly available epinephrine, therefore, is a mixture of these two hormones (usually 10-20%

norepinephrine) and its effects are a resultant of the combined actions of these two hormones.

Since these hormones possess an asymmetric carbon atom, two stereoisomers are possible for each one of them. The naturally-occurring epinephrine is the L-isomer and is levorotatory.

Functions. In general, the adrenal medullary hormones reinforce the functions performed by the sympathetic nervous system. Although both these hormones exert similar effects in regulating carbohydrate metabolism and blood pressure, yet epinephrine is more closely related to carbohydrate metabolism and norepinephrine to blood pressure. *Epinephrine* conducts a wide variety of functions, which are as follows:

1. It promotes glycogenolysis in muscles and liver, resulting in an increase of blood glucose level and an increased lactic acid formation in muscles. These changes are then followed by an increase in oxygen consumption.

2. It causes an increase in blood pressure because of arteriolar vasoconstriction of the skin and splanchnic vessels.

3. It brings about an increase in the heart rate and in the cardiac output.

4. It causes dilation of vessels (= vasodilation) of skeletal muscles, corona and the viscera. This results in an increase of blood flow in these areas.

5. It relaxes the muscles of gastrointestinal tract and bronchials of the lungs but causes contraction of the pyloric and ileocecal sphincter muscles.

6. It also serves in cases of emergency. Under emotional stress, fear or anger, it is secreted in the blood stream and the blood is shifted from the viscera to the brain and the muscles so that the individual becomes ready for fight. It is for this reason that the adrenals are frequently referred to as the '*emergency glands*' or the '*glands of flight*, fright and fight' and the two adrenal medullary hormones as **'emergency hormones'**.

Norepinephrine, on the other hand, does not relax bronchiolar muscles and has little effect on cardiac output. It augments both systolic and diastolic blood pressure.

Adrenal demedullation. Despite the varied and definite physiologic effects of its characteristic hormones, the adrenal medulla does not appear to be essential to life. Hence, removal of only the medullary portion of the adrenal gland leads to no specific physiologic disorder. This is because the autonomous nervous system may take over in its absence. Consequently, the exact importance of the adrenal medulla is really undetermined. However, certain tumours of the medullary cells result in **pheochromocytoma**, characterized by hypertension and ultimately leading to death due to coronary insufficiency and pulmonary edema. Treatment is to remove the tumour surgically.

STEROID HORMONES

These include the sex hormones and the hormones from adrenal cortex. These are synthesized in mammals by the ovary (or testis), adrenal cortex, corpus luteum and the placenta. The activity of sex hormones appears to be controlled by the hormones secreted by the anterior lobe of the hypophysis (= adenohypophysis). Because of this, the sex hormones are, sometimes, referred to as *secondary sex hormones* and the hormones of the adenohypophysis, which are of proteinaceous nature, are called as *primary sex hormones*. Three types of sex hormones are recognized:

(*a*) the estrogens (female or ovarian or follicular hormones)

(*b*) the androgens (male or testicular hormones)

(*c*) the gestogens (corpus luteal hormones).

The sex hormones are concerned with the sexual processes and the development of secondary characteristics which differentiate males from females. The adrenal cortical hormones perform a variety of important functions related to cell metabolism. Based on the number of carbon atoms present in the molecule, the steroid hormones may be named as C18, C19 or C21 steroids.

C18 STEROIDS

1. Ovarian Hormones Structure. Mammalian ovary contains ovarian follicles and corpus lutea. Hormones produced mainly in the follicles are known as estrogens (*oistros*G = a gadfly, hence sting or frenzy). "Estrogen is a generic term for a substance that induces estrus, which is a cyclic phenomenon of the female reproductive system. The stages and timings differ in various species but, in general, first a *proestrus* period occurs, during which the follicle repens and the organs of reproduction develop. This is followed by *estrus*, the period of heat, in which the female will receive the male. Ovulation takes place toward the end of estrus, either spontaneously or, as in rabbit, after mating. Then follows a period of

retrogression of the accessory reproductive organs and a period of sexual inactivity".

Chemically, the estrogens are derivatives of a C18 hydrocarbon, estrane (figure 12).

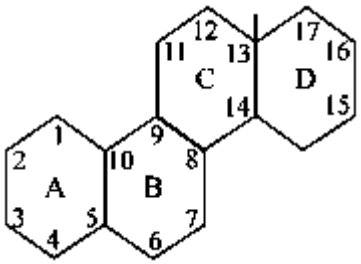


Figure. 12. Structure of estrange

The three compounds of this group (figure 13) with hormonal activity are:

1. β-estradiol (= dihydrotheelin), $C_{18}H_{24}O_2$
2. Estriol (= theelol), $C_{18}H_{24}O_3$
3. Estrone (= theelin), $C_{18}H_{22}O_2$

Estrone is the first known member of the sex hormones and was isolated by Adolf Butenandt and Doisy independently in 1929 from the urine of pregnant women. A year later, the estriol was isolated from human pregnancy urine by Marrian. Later, the estradiol was also isolated.

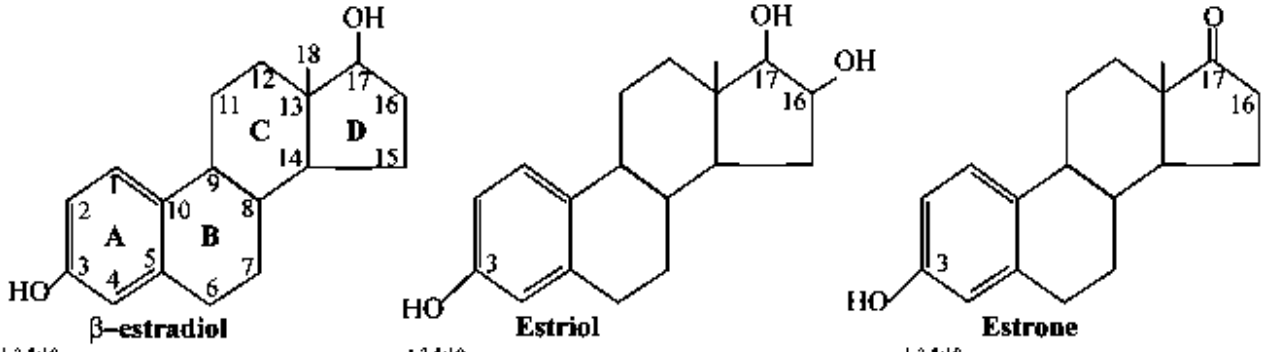


Figure 13. Structures of β-estradiol, estriol and estrone

All these are characterized by the absence of a CH_3 group at carbon 10 and by the aromatic nature of ring A, making the OH group phenolic in character. Of all these, b-estradiol is most potent physiologically, estrone less potent and estriol is least active. Their relative potencies are 50:5:1 respectively. Although ovary is the chief source of esrognes, they are in smaller amounts also produced by the testis and the adrenal cortex. Estrogen production is highest when a woman is young and slows down with age, giving rise to menopausal symptoms. The symptoms vary with each women. By 40's, women enter perimenopause, when menstruation becomes less regular, skin becomes dryer, hair turn brittle and sparser; women may feel a loss of libido and may suffer fluctuations in mood. Menopause follows, on an average between 45 and 50 years of age. Heavy women have an advantage over the slim ones. Their fat cells manufacture a form of estrogen called estrone, even after estrogen from ovaries shuts off.

***Biosynthesis*.** In nonepregnant females, estrogen is mainly synthesized in the ovary. The estrogen (as well as the androgen) are, in part, transported by binding to a specific plasma protein called sex steriod binding protein SBT. The amount of this protein increases in pregnancy or estrogen therapy which results in reduced androgenic action. Curiously enough, testosterone, a male hormone, is the precursor of estrogens. Figure 14 depicts the probable pathway of estrogen synthesis.

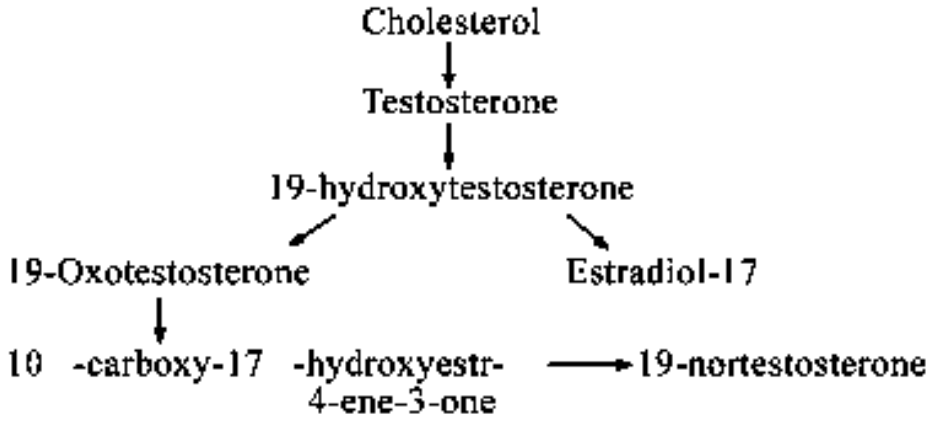


Figure 14. Probable pathway of estrogen synthesis

Metabolism. Most of the metabolic reactions of the estrogens (*i.e*, the interconversion reactions of all the three forms) take place in the liver as follows (figure 15):

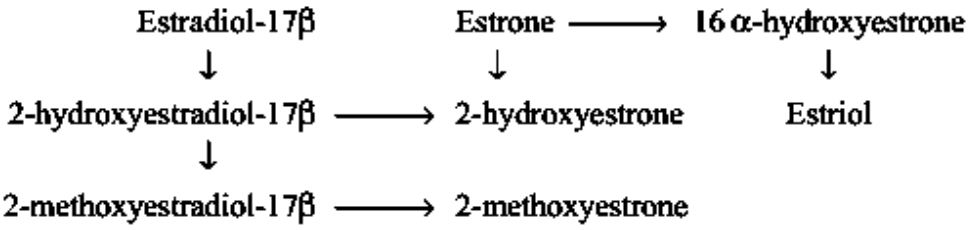


Figure 15. Estrogens metabolism

Estriol is the principal estrogen found in the placenta and urine of pregnant females. It is produced by hydroxylation of estrone at C16 and reduction of keto group at C17.

Functions. "In women, the follicular hormones (estrogens) prepare the uterine mucosa for the later action of the progestational hormones (produced by the corpus luteum). The changes in the uterine include proliferative growth of the lining of the endometrium, deepening of uterine glands, and increased vascularity; changes in the epithelium of the fallopian tubes and of the vagina also occur. All of these changes begin immediately after menstrual bleeding has ceased."

Estrogen preserves the elasticity of the skin and possibly improves the memory in women at postmenopausal stages. It also protects women from osteoporosis by slowing the rate at which calcium is leached from their bones. Estrogen supplement also preserves the flexibility of blood vessels, thus helping to prevent cardiac diseases. Nowadays, estrogen in combination with the hormone progestin is considered an important tool for helping women remain healthy. The combination is known as **hormone replacement therapy (HRT)**, which has indeed become the closest in medicine to a woman's elixir of youth. HRT, when used by menopausal women, relieves hot splashes, dry sweats and vaginal dryness. However, the long-term use of HRT or estrogen therapy hightens the risk of ovarian cancer.

It was cleary shown the effect of estrogen on two brain areas, commonly associated with memory and learning, the hippocampus and cerebral cortex. She found that ovariectomized female rats given estrogen had more of an enzyme called *choline acetyltransferase (ChAT)* in the hippocampus and cerebral cortex than control animals did. ChAT enchances the working of the cells in basal forebrain because ChAT makes acetylcholine (ACh) which helps nervous communication with other nerve cells. In a nutshell, *estrogen enchances brain power*. Estrogens could also protect brain cells from toxins. Estrogens can also act as an antioxidant soaking up highly reactive molecules called free radicals which can kill a cell by fracturing its membrane lipids, proteins and DNA. Estogen is also being widely perceived to have a significant effect (of improving verbal memory) on patients with Alzheimer's disease.

The estrogens are also effective in the development of *secondary sex characters in females*. These are listed in Table 2.

Table 2

Secondary sex characters in females

Characters	*Changes*
1. External genitalia	Enlargement of uterus and vagina; Widening of pelvis.
2. Internal genitalia	Periodic vaginal bleeding that occurs with the shedding of the uterine mucosa (i.e., menstruation).
3. Voice	Larynx retains its prepubertal proportions, i.e., small in size; Voice stays high-pitched.
4. Hair growth	Less body hair and more scalp hair; Hair line on scalp resembles that of a child and does not recede anterolaterally (Fig. 30–10); Hair appear in axillae (axillary hair) and around vagina; Pubic hair have a characteristic female pattern, i.e., flat-topped; Hair on face absent i.e., no beard.
5. Mental	Less aggressive; Passive attitude; Interest in opposite sex less pronounced.
6. Body conformation	Narrow shoulders and broad hips, which are popularly called as 'hip pads'; Thighs that converge and arms that diverge, i.e., a wide carrying angle; Distribution of fat in the breasts and buttocks takes place, leading to their enlargementÅthe breasts also have high pigmentation in the areola which becomes even more intense during the first pregnancy; Muscles not pronounced.
7. Skin	Sebaceous gland secretions become more fluid and thus counter the effect of testosterone and inhibit formation of comedones ('black-heads') and acne (a hard, red inflamed pimple)
8. Weight gain	Tend to gain weight from the waist down.

C 19 STEROIDS

Testicular Hormones Structure. These hormones are secreted mainly by the testes, the male reproductive organs and are called as androgens (*andros*G = male). Chemically, these are derivatives of a C19 hydrocarbon, *androstane* (figure 16).

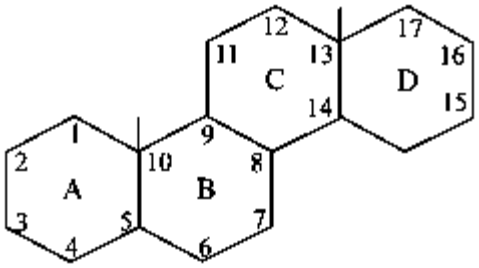


Figure 16. Structure of androstane

There are many hormones secreted from testes with androgenic activity. The three important ones (figure 17) are:

1. Testosterone, C19H28O2
2. Androsterone, C19H30O2
3. Dehydroepiandrosterone, C19H25O2

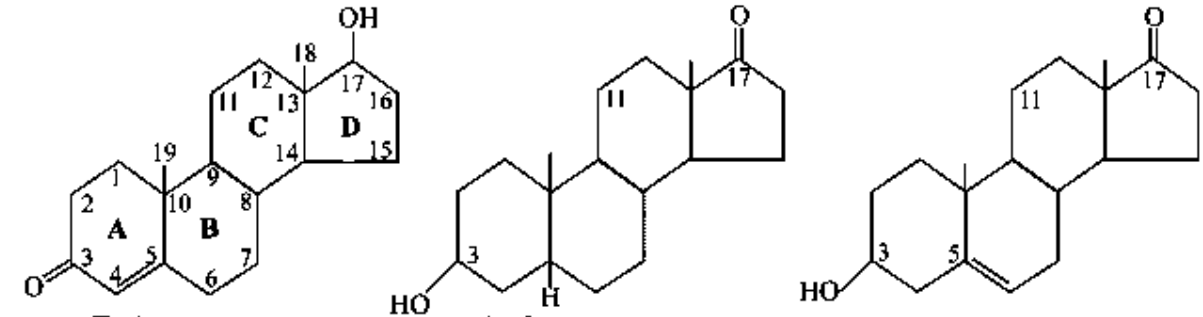


Figure 17. Structure of testosterone, androsterone, dehydroepiandrosterone

Androsterone was first isolated by Adolf Butenandt *et al* in 1931 from male urine (about 15 mg from 15,000 litres of urine). Testosterone is most potent of all these and dehydroepiandrosterone is least active. The relative potency ratio of

these three forms is 20:7:1. Testosterone has a tendency to rise during late summer and early fall to peak in September. DHEA production peaks between ages 25 and 30 and wanes with age. Restoring DHEA levels to peak is said to boost the immune system.

A few testicular hormones are also produced by the adrenal gland. The structure of two such hormones is given in figure 18

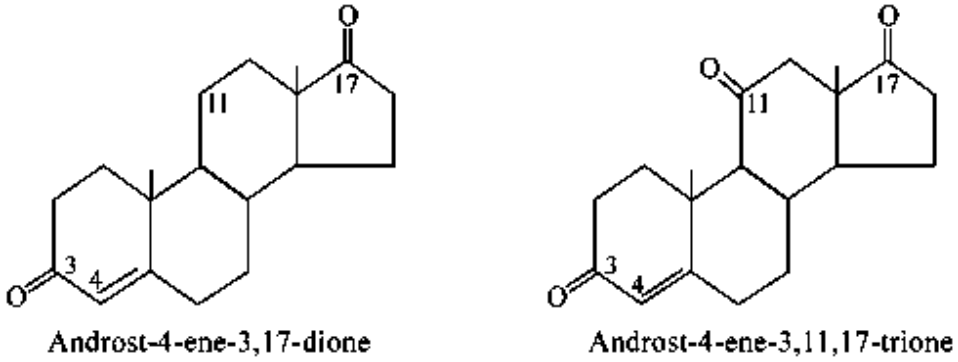


Figure 18. Testicular hormones produced by the adrenal gland

***Biosynthesis*.** In figure 19 biosynthesis of testosterone from cholesterol has been depicted. The principal male hormone, testosterone, is synthesized by the Leydig cells of the testes from cholesterol through pregnenolone, progesterone and hydroxyprogesterone. The latter is then converted to a C19 ketosteroid called androstenedione which is the immediate precursor of testosterone. It is presumed that the same sequence of events also takes place in the adrenal gland, ovary and placenta.

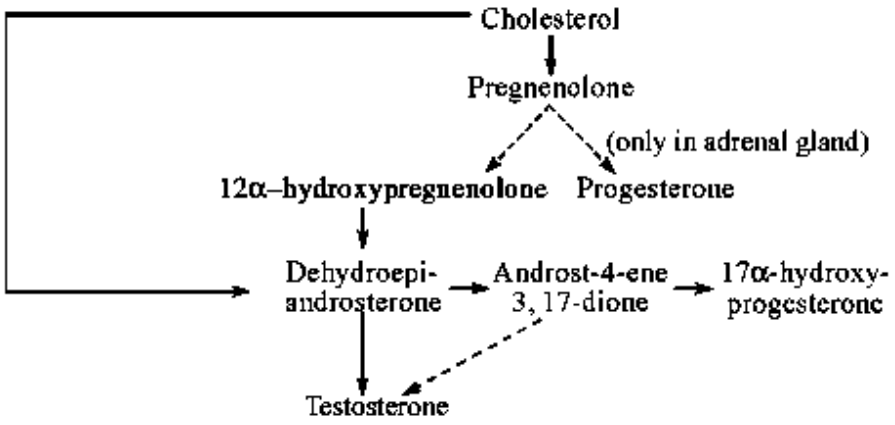


Figure 19. Biosynthesis of Testosterone

In addition to testosterone, adrostenedione and DHEA are also synthesized in the testes, although in amounts far less than that of testosterone. In normal male, 4 to 12 mg of testosterone are secreted each day. The amount of DHEA secreted is, however, greater than that of testosterone (approximately 15 to 50 mg/day).

Metabolism. Most of the metabolic transformations of androgens takes place in the liver. In some mammals like rats, these reactions occur mainly in the bile and urine. Two major reactions occurring in the liver are:

(*a*) Conversion of testosterone to androst-4-ene-3,17-dione.

(*b*) Interconversion of 3-hydroxy and 3-keto derivatives.

Functions. Testosterone has often been considered to be a 'youth horomone', because of its effects on the musculature, and it is occasionally used for treatment of persons who have poorly developed muscles. Because of the ability of testosterone to increase the size and strength of bones, it is often used in old age to treat osteoporosis. Like estrogens, the androgens are also responsible for the development of secondary sex characters in males. These are listed in Table 3.

Table 3

Secondary sex characters in males

Characters	*Changes*
1. External genitalia	Penis increases in length and width; Scrotum becomes pigmented and rugose.
2. Internal genitalia	Seminal vesicles enlarge and secrete– they also begin to form fructose ; Prostate and bulbourethral glands also enlarge and secrete.
3. Voice	Larynx enlarges and the vocal cords increase in length and thickness; Voice becomes deeper.
4. Hair growth	General body hair increases; Hair line on scalp recedes anterolaterally (Fig. 31–10); Hair appear in axillae (axillary hair) and around anus; Pubic hair have a characteristic male pattern, i.e., triangle with apex up; Hair on face grow as beard.
5. Mental	More aggressive; Active attitude; Interest in opposite sex more pronounced.
6. Body conformation	Shoulders broaden and hips remain unaltered, i.e., narrow; Thighs that diverge and arms that converge, i.e., a narrow carrying angle; No distribution of body fat in the chests and buttocks; Muscles enlarge, leading to a muscular body contour.
7. Skin	Sebaceous gland secretion thickens and increases (predisposing to acne).
8. Weight gain	Tend to gain weight in the abdominal region.

Androgens regulate the activities of the male reproductive system; estrogens stimulate the growth, maturation and maintenance of the female reproductive system and accessory sex tissues. However, both androgens and estrogens also have significant effects on the non-reproductive tissues of the body. For instance, androgens stimulate the growth of skeletal muscles. Androgens and certain androgen derivatives (collectively called as **anabolic steroids**) are often used by weight lifters, wrestlers and football players to increase muscle mass and strength. Anabolic streroids are also used by female athletes, probably with advantage; however, they produce other masculinizing effects as well.

The androgens constitute one factor in the production of baldness. Age and inheritence are other factors involved in causing this condition. But baldness does not ensue without androgenic stimulation. In cases where the testes fail to descend in a normal manner (cryptorchidism), the testosterone is of considerable value. But the long usage and higher dosage of testosterone (*e.g.*, 25 mg per day for 4−6 weeks) in individuals often leads to atrophy of the sperm. The effect can, however be reversed by discontinuing the treatment for a similar period. Testosterone also controls the libido, and also the development of muscle mass and bone density

C 21 STEROIDS

3. Adrenal Cortical Hormones Secretory gland. The adrenals (*ad* = at; *renal* = pertaining to kidneys)or suprarenal glands in all tetrapods are a pair of glands, so named because of their position very close to or at the top of the kidneys. Each of the two adrenals among mammals is actually a '*double gland*' and is composed of 2 distinct parts: namely an outer barlike covering called the cortex, surrounding an inner corelike dark-coloured mass called the medulla. The cortex is derived from the mesodermal glandular tissue and the medulla originates from the cells of neural crest. Both these parts secrete hormones which differ from each other chemically as well as physiologically. Hence, these 2 components are

discussed separately. In man, the adrenals are two small structures sitting like ‘cocked hats’over the apical end of the kidneys and each gland weighs about 3 grams.

When there is prolonged stimulation of the adrenal cortex by adrenocorticotropic hormone (ACTH), the middle and inner zones both hypertrophy; but a total lack of ACTH causes these two zones to atrophy almost entirely, leaving the outer zona glomerulosa partially intact. On the other hand, enhanced aldosterone production causes hypertrophy of the zona glomerulosa, while the other two zones remain almost unaffected.

Structure. Adrenal cortex secretes some 40-50 closely related C21 steroids, collectively called as corticosteroids (refer figure 20).

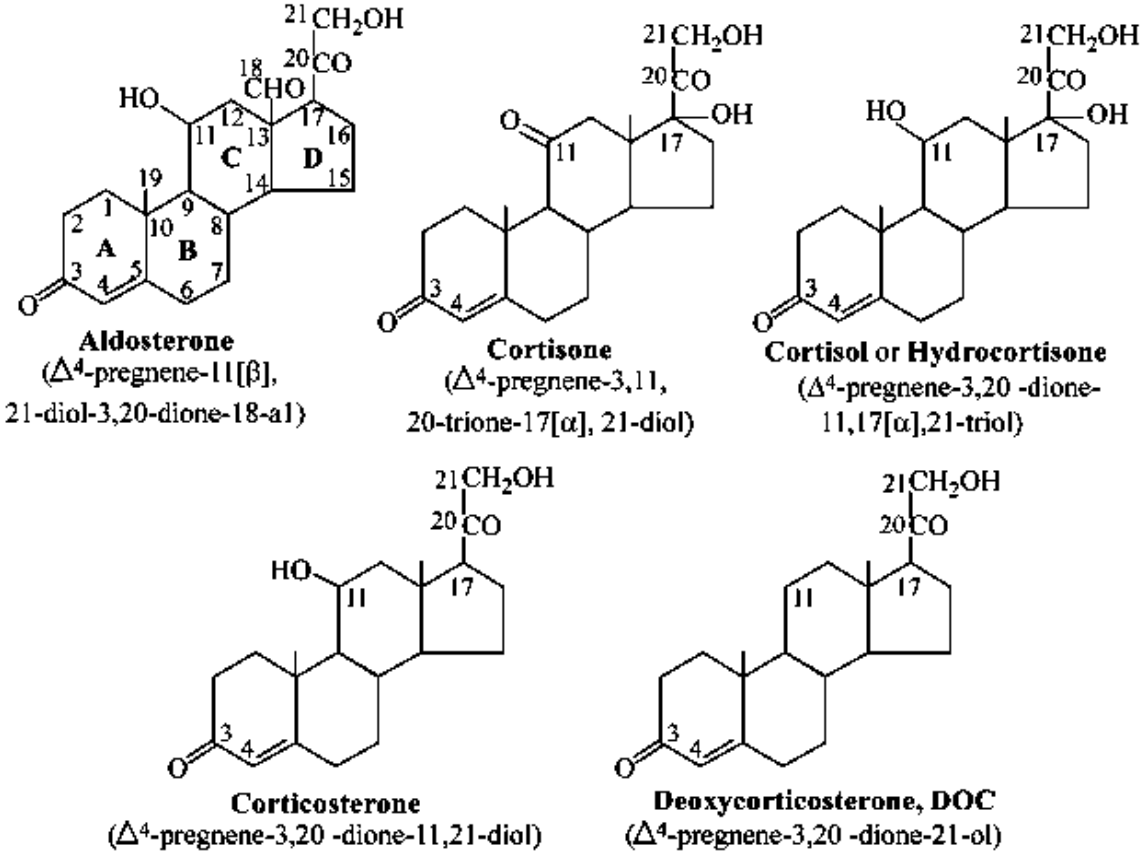


Figure 20. Structures of corticosteroids

From physiological viewpoint, the corticosteroids may be grouped under two categories:

A. *Mineralocorticoids.* — concerned primarily with the transport of electrolytes and the distribution of water in tissues, *e.g.*, aldosterone and deoxycorticosterone.

B. *Glucocorticoids*.—concerned primarily with the metabolism of carbohydrates, proteins and fats, *e.g.*, cortisone (= compound E), cortisol (= hydrocortisone) and corticosterone.

However, during periods of stress, the amount of cortisol released during 24 hours may increase even up to 300 mg. The release of cortisol by the adrenal cortex has a diurnal rhythm. More is released during the day than during the night. Their structure is given in figure 20. Aldosterone is 30 times more active than deoxycorticosterone. Deoxycorticosterone, in its turn, is 4 times more potent than cortisone and cortisol in maintenance of life. Corticosterone is least active in this regard.

Functions. A *mineralocorticoid*, aldosterone is chiefly concerned with water-salt balance of the body. It stimulates the reabsorption of Na+ ion from the kidney tubules and as such regulates NaCl contents of the blood. This also causes excretion of K in the urine. Aldosterone is also more potent in maintaining the life of adrenalectomized animals.

Glucocorticoids, on the contrary, govern many other processes. They perform the following physiological functions:

1. Influence the carbohydrate metabolism firstly by increasing release of glucose from the liver and secondly by promoting the transformation of amino acids to carbohydrates.

2. Inhibit protein synthesis in muscle tissues.

3. Control eosinophil cells of the blood.

4. Regulate lipogenesis.

5. Reduce the osteoid matrix of bone, thus favouring osteoporosis (weak bones) and heavy loss of calcium from the body.

6. Decrease immune responses associated with infection and anaphylaxis (immunosuppressive effects).

7. Cause increased secretion of hydrochloric acid and pespinogen by the stomach and that of trypsinogen by the pancreas (exocrine secretory effects).

8. Cause retention of sodium(and water) and loss of potassium to some extent. In this respect, it resembles aldosterone in action.

Hypoadrenocorticism. A decrease in the amount of corticosteroids in the body (hypoadrenocorticism) leads to the decreased metabolic rate, excessive pigmentation, loss of appetite (anorexia), muscular weakness, deficiency of blood (anemia), eosinophilia and decreased blood sugar (hypoglycemia) with fasting.

Hyperadrenocorticism. The excessive supply of adrenal cortical steroids (hyperadrenocorticism) results from cortical cell tumours which may arise in or outside the adrenal gland. Oversecretion of cortisol in man leads to a rare disease, **Cushing's syndrome**, after its discoverer, Harvey Cushing. The most common cause of the symptoms of Cushing's syndrome is the prolonged administration of glucocorticoids for medical treatment. The syndrome is characterized by profound disturbance of carbohydrate, protein, fat and calcium metabolism. There occurs mobilization of fat from the lower part of the body, with the concomitant extra deposition of fat in the thoracic region. The obesity becomes visible on the neck (buffalo hump) and on the face (moon face). Weakness and muscle wastings with marked osteosis become evident. Hypertension, pigmentation of the hair and excessive growth of hair are other symptoms. In men, there is impotence, and in women, amenorrhea and masculinization. Thus, Cushing's syndrome resembles somewhat adrenogenital syndrome. Hypersecretion of aldosterone leads to a marked Na+ and water retention, resulting in edema and hypertension causing heart failure. The adrenal cortex also produces androgenic steroids known as *adrenosterones*. Their hypersecretion has effects varying according to the age and

sex of the patient. In adult female, it leads to **adrenal virilism.** In it menstruation stops, breasts atrophy, hair on breast and face develop and the voice deepens. In all, the adult woman becomes masculine. In adult males, there occurs excessive hair growth, enlargement of the sex organ and increased sexual desire. However, in children excessive supply of adrenosterones results in precocious development of sex organs and the secondary sexual characters.

Adrenal decortication. Removal of adrenal cortex (*adrenalectomy*) leads to a fatal human disease known as **Addison's disease**, named after its discoverer Thomas Addison.

Many of the symptoms of this syndrome resemble those of adrenalectomized animals. Addison (1855) described these in his own words as follows: "The leading and characteristic features of the morbid state to which I would direct attention are anemia, general langour and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of colour in the skin, occurring in connection with a *diseased* condition of the 'supra-renal' capsules".

Other symptoms now attributed to this disease are low blood pressure, lowered basal metabolic rate (BMR), subnormal temperature and a disturbed water and electrolyte balance. This includes loss of sodium and chloride ions and a loss of body water. The person develops hyperkalemia and acidosis because of failure of potassium and hydrogen ions to be secreted in exchange for sodium reabsorption.

The patient becomes hypoglycemic. The kidneys are also affected, resulting in urea retention. Skin pigmentation occurs in areas of greatest normal pigmentation. Frequently, the face and neck and backs of the hands are so deeply bronzed as to cause the afflicted individual to look like a mulatto.

The melanin is not always deposited evenly but occasionally in blotches and especially in the thin skin areas such as the mucous membranes of the lips and the thin skin of the nipples. Thus, the chief symptoms of this syndrome are: anorexia,

emesis (= vomiting), diarrhea, anemia, deep pigmentation of the buccal cavity and nipples, rapid loss of weight, excessive loss of NaCl in the urine and low blood pressure. As the extracellular fluid becomes depleted, the plasma volume falls, the concentration of R.B.C. rises markedly, the cardiac output lowers down and the patient dies in shock. The grip of Addisonian patients on their life is tenuous and any stress, infection, cold or even noise can precipitate a crisis leading to death. Addisonian patients may be cured by giving extracts of the adrenal cortex. This has been very successful since its beginning in about 1929. Because this is substitution therapy, like most endocrine therapy, the constant administration of potent extracts is essential. Loeb (1939) has, however, demonstrated that NaCl is of immense value to Addisonian patients as it corrects the electrolyte and water imbalance in them. The administration of deoxycorticosterone (usually as acetate) or aldosterone also cures the disease.

4. Corpus Luteal Hormones Structure. The hormones secreted by the ovarian bed, corpus luteum are collectively called as **gestogens** or **progestins**. The principal gestogen is progesterone (the two pregnenolones, 20α-OH and 20β-OH are other hormones secreted by the corpus luteum). Progesterone is a C21 steroid and is secreted by the corpus luteum during the second half of the menstrual cycle. This was first isolated in pure form by Adolf Butenandt *et al* (1934) from corpus lutea of pregnant sows. It has also been isolated from adrenal cortical extracts. But its presence in the adrenal tissue is a consequence of its role as an intermediate in the biosynthesis of the typical adrenal cortical hormones. Chemically, progesterone is one of the pregnane derivatives and lacks the ketol group. Its molecular formula is $C_{21}H_{30}O_2$ (figure 21). It closely resembles deoxycorticosterone in structure. It is, therefore, not surprising to find progesterone with certain adrenocortical properties, *viz*., those influencing salt and water. Indeed, it serves as a procursor of the steroidal adrenocorticoids. It is soluble in most organic solvents and in vegetable oils but is insoluble in water.

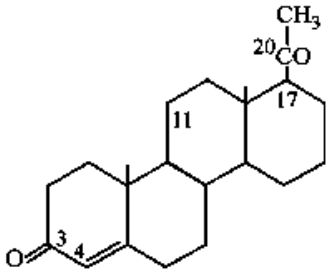


Figure 21. Structure progesterone

Biosynthesis. Progesterone is synthesized in the corpus luteum, placenta and the adrenal cortex from its immediate precursor, pregnenolone by a combined dehydrogenase and isomerase reaction.

Metabolism. The metabolic fate of progesterone has been studied by injecting C14 – labeled hormone. About 75% of the injected progesterone is translocated to the intestine *via* bile and passed out in feces. A 20-hydroxy compound, pregnanediol, is the main urinary product of progesterone metabolism in human beings and rabbits. Such a conversion of progesterone into pregnanediol is not carried out in rat liver.

Functions. Progesterone has manifold functions:

1. The primary function of progesterone is to promote the proliferation of uterine mucosa so that the latter may receive the fertilized ovum. It, thus, serves for implantation of the fertilized ovum. If pregnancy ensues, continued secretion of progesterone is essential for completion of term.

2. It brings mammary glands to full maturity during gestation (pregnancy) for their onward use in breast-feeding by the newborn

3. It also maintains the uterus quiescent during pregnancy (*i.e.*, inhibits contraction of the uterus).

4. If given between 5th and 25th day of the normal menstrual cycle, progesterone exerts an antiovulatory effect. This is the basis for the use of certain progestins as oral contraceptive agents.

5. It serves as precursor of cortisol and corticosterone in the adrenal glands.

PARAHORMONES OR TISSUE HORMONES

In addition to the hormones discussed in the preceding pages, a number of others have been found to possess hormonal properties. These compounds are effective at low concentrations; unlike global hormones, they are not transported between tissues in the blood, but act on the tissue in which they are produced. They are, hence, also called as **tissue hormones**. They are at best local hormones because they are short-lived and are *paracrine* rather than endocrine in nature, but they fit the definition of hormone. They alter the activities of the cells in which they are synthesized and of adjoining cells. The nature of these effects may vary from one type of cell to another, in contrast with the more uniform actions of global hormones such as insulin or glucagon. Four such hormones (or groups of hormones), whose hormonal function has been established, are : *melatonin, renal hormones, eicosanoids and opiate peptides.*

Eicosanoid Hormones

A. Structure and Metabolic Roles. Eicosanoid hormones (or simply eicosanoids) are fatty acid derivatives with a variety of extremely potent hormonelike actions on various tissues of vertebrates. Eicosanoids, in general, are known to be involved in reproductive function; in the inflammation, fever and pain ; in the formation of blood clots and the regulation of blood pressure ; in gastric acid secretion ; and in a variety of other human processes.

Eicosanoids are all derived form 20-carbon polyunsaturated fatty acid, **arachidonic acid** (20:4; 5,8,11,14), from which they take their general name (*eikosi*G = twenty). There are 3 classes of eicosanoids (or the *signal molecules*, as they are also called) : prostaglandins, prostacyclins and thromboxanes, and leukotrienes (figure 22).

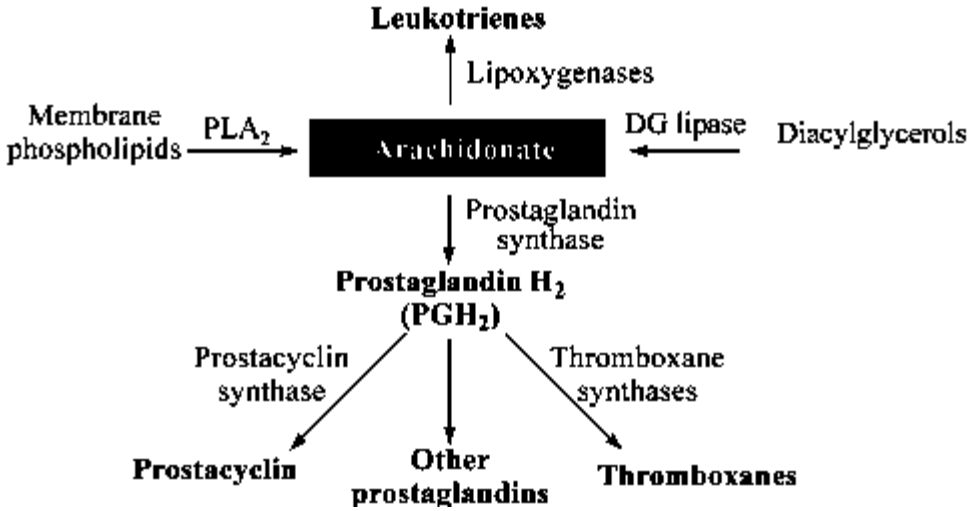


Figure 22. Biosynthesis of eicosanoids

Prostaglandins.

Kurzrok and Lieb (1930), for the first time, observed that the human semen is able to bring about strong muscular contraction or relaxation when placed in the uterus. This is due to the presence in the semen of a number of structurallyrelated compounds collectively termed prostaglandins. The name prostaglandin (abbreviated as PG) was first given by a Swedish chemist U.S. von Euler in 1935 to this lipid-soluble acidic substance. Although prostaglandins were originally found in the seminal fluid of man and other species (hence the nomenclature) but now these have been found to occur in a wide variety of mammalian tissues including brain, spinal cord, thymus, lungs, pancreas, kidneys, menstrual fluid and placenta. However, *semen remains one of the richest sources of prostaglandins as yet.* Chemically, the prostaglandins resemble prostanoic acid (figure 23). They are hydroxy derivatives of the polyunsaturated C-20 cyclic fatty acids. In its molecule, the carbon atoms 8 to 12 are involved in the formation of a 5-carbon ring called cyclopentane ring. Variations in the double bonds and in the hydroxyl and ketone groups give rise to prostaglandins that can be divided into 9 groups designated as A through I (and accordingly, the prostaglandins are designated as PGA through PGI). The PG, obviously, stands for prostaglandin and the third capital letter, in most cases, indicates the type of the substituents found on the hydrocarbon chain.

In fact, two groups of prostaglandins were originally recognized: **PGE** which is ether-soluble (hence the nomenclature, E from ether) and has a keto group at C9, and **PGF** which is phosphate-buffer-soluble (hence the nomenclature, F from *fosfat* in Swedish) and has a hydroxyl group at C9. There are 3 compounds from each of these two groups, arising from eicosanoic (*i.e*., C20) fatty acids with 3, 4 or 5 double bonds. These are the 6 primary prostaglandins and are abbreviated as PGE 1, PGE2, PGE3, PGF1 α, PGF2α and PGF3α. In the abbreviations of the prostaglandins, the number 1, 2, 3 is added as subscript to indicate the number of carbon-carbon double bonds outside the ring. When there is more than one member, the group is subdivided into α, β, γ etc. These occur in most cells. Their structure appears in Fig. 30−60 along with their biosynthetic origin. In addition to these, there are several secondary prostaglandins that are derived from PGE types through enzymic conversions. Prostaglandins have a half life of 5 minutes or less, hence they are destroyed very rapidly in the body. They have, therefore, *a high turnover rate.* The short half-life of these tissue hormones is thought to ensure their transient and limited response at the intermediate site of production. From a medical viewpoint, they are potentially the most revolutionary therapeutic substances yet discovered. Prostaglandins affect smooth muscles and blood pressure and often the activities of individual prostaglandins oppose one another. For example, prostaglandin E2 (PGE2) dilates blood vessels and bronchi, and prostaglandin F2α (PGF2α) constricts these smooth muscle tissues. The prostaglandins perform a wide variety of biologic activities:

1. As mentioned earlier, they bring about contraction or relaxation of the smooth muscles of the uterus, *esp*., at the time of ovulation. This may be due to a chelation of calcium ions. As little as 1 ng/ml can cause contraction of the smooth muscles. They, thus, resemble ocytocin in this regard. They are modulators of hormone action.

2. They lower down blood pressure.

3. They inhibit lipolysis in adipose tissue, possibly by inhibiting the conversion of ATP to cyclic AMP and inhibition of platelet aggregation. The prostaglandins, thus, have the opposite effect of epinephrine, norepinephrine, glucagon and corticotropin on the release of fatty acids from adipose tissue.

4. They behave both as pressor and depressor agents under different conditions and thus affect the cardiovascular system.

5. They appear to control the secretion of gastric hydrochloric acid.

6. They also have some beneficial effect in the control of the acid-induced gastric ulcers.

7. Prostaglandins are best known for their effects on reproductive system. There seems to be a strong link between male fertility and seminal prostaglandin content. Human semen is rich in prostaglandins, which when deposited in vagina through coitus, facilitate conception. Thus, low prostaglandin content in the human semen is related to infertility.

8. They are effective labour inducers in pregnant women also.

9. Recent work indicates that the prostaglandins are also involved in the inflammatory reaction and pain. Anti-inflammatory drugs such as aspirin, in part, act by inhibiting the synthesis of prostaglandins. However, paracetamol (an analgesic drug like aspirin) is not anti-inflammatory as it does not inhibit the synthesis of prostaglandins. The widespread distribution of prostaglandins and their capacity to carry out varied metabolic effects have, however, led some to question the propriety of their being called hormones.

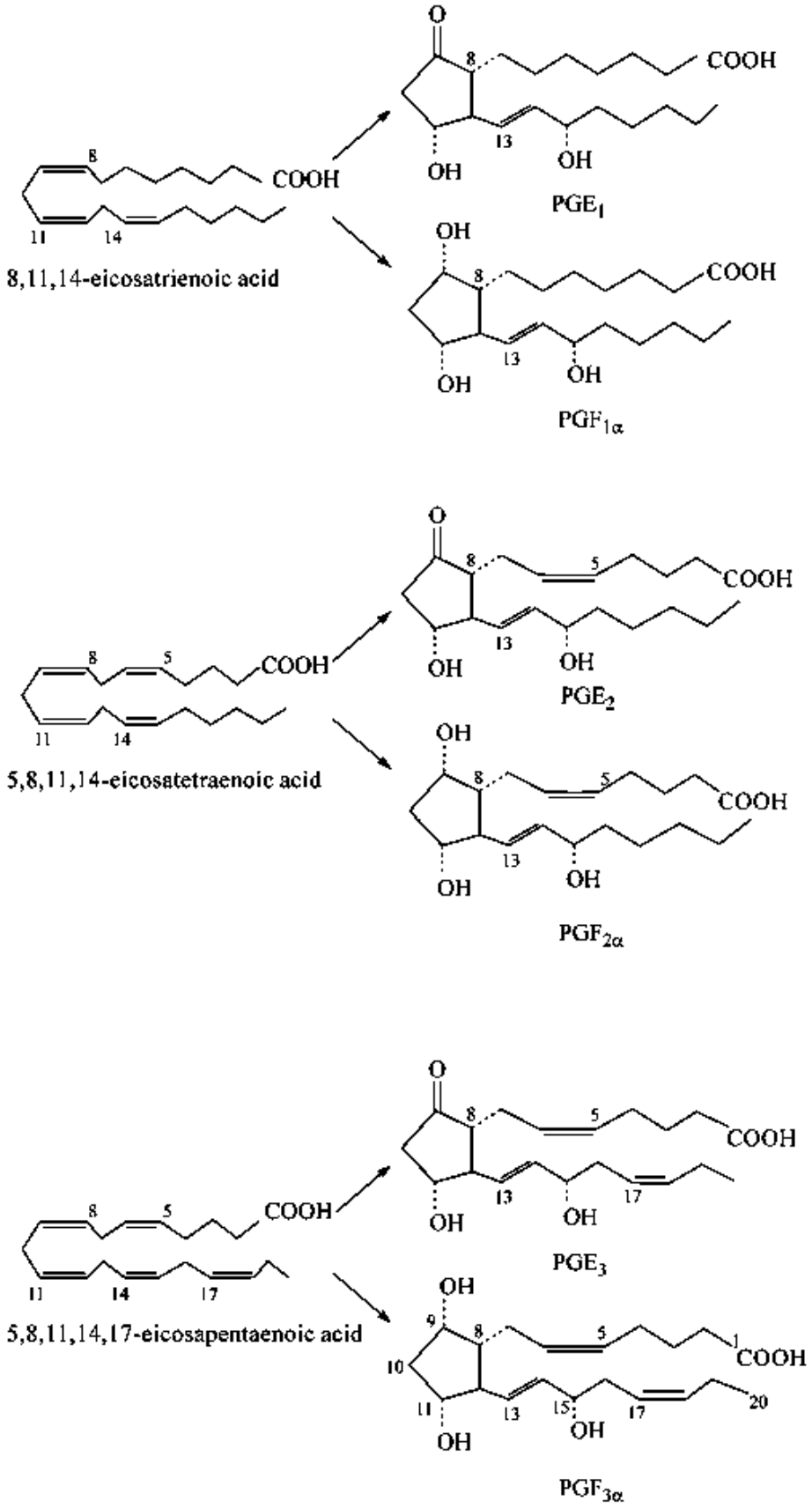


Figure 23. Biosynthesis of prostaglandines

Thromboxanes and Prostacyclins

Thromboxanes (TXAs) and prostacyclins (PGIs) are structurally-related compounds that arise from a nascent prostaglandin. In compounds of both these categories, carbons 8 and 12 are joined and an oxygen atom is added to form the six-membered ring (*cf* prostaglandins, where a five- membered ring is formed).

Thromboxane A2 (TXA2) was first isolated, in 1975, by Samuelsson *et al* from blood platelets (also known as thrombocytes, hence the nomenclature). The following year, John Vane and colleagues at the Royal College of Surgeons, London identified yet another type of eicosanoid **prostacyclin I2** (PGI2), which is produced primarily in vascular tissues, *i.e*., blood vessels. The striking similarity and diversity in the physiological roles of thromboxanes and prostacyclins displays a critical balance required for the normal functioning in the body. TXA2 and PGI2 are medically important examples of how such a balance operates *in vivo*. TXA2 is a highly effective vasoconstrictor (blood vessel constrictor) and platelet aggregator ; conversely, PGI2 is a potent vasodilator and inhibitor of platelet aggregation. Platelets are the blood cells that first appear and aggregate at the site of injury to produce a temporary plug that serves as a base on which the strong fibrin clot ultimately forms. However, for maintenance of normal blood flow, TXA2-induced aggregation of platelets would quickly prove fatal. Thus, a vital opposing role of PGI2 is to prevent platelets from aggregating on blood vessel walls, a site of PGI2 production.

Unlike other eicosanoids, PGI2 is not metabolized during passage through the lungs. Thus, TXA2 and PGI 2 are continuously engaged in a ‘tug of war’ with respect to platelet aggregation (figure 24)

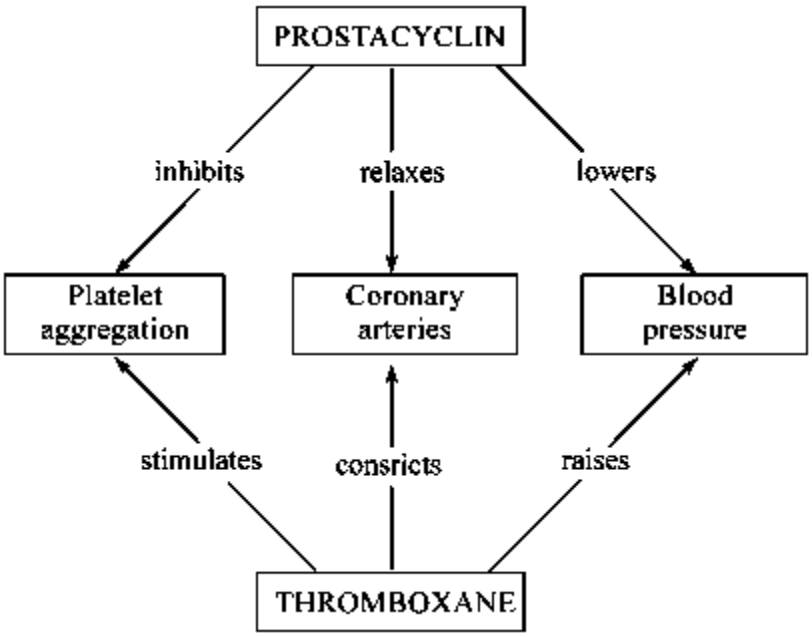


Figure 24. Effects of prostacyclin and thromboxane

Leukotrienes.

Leukotrienes (LTs), first found in leukocytes, are cysteinyl-containing derivatives of arachidonic acid with a series of three conjugated double bonds in its molecule (figure 25), hence their nomenclature.

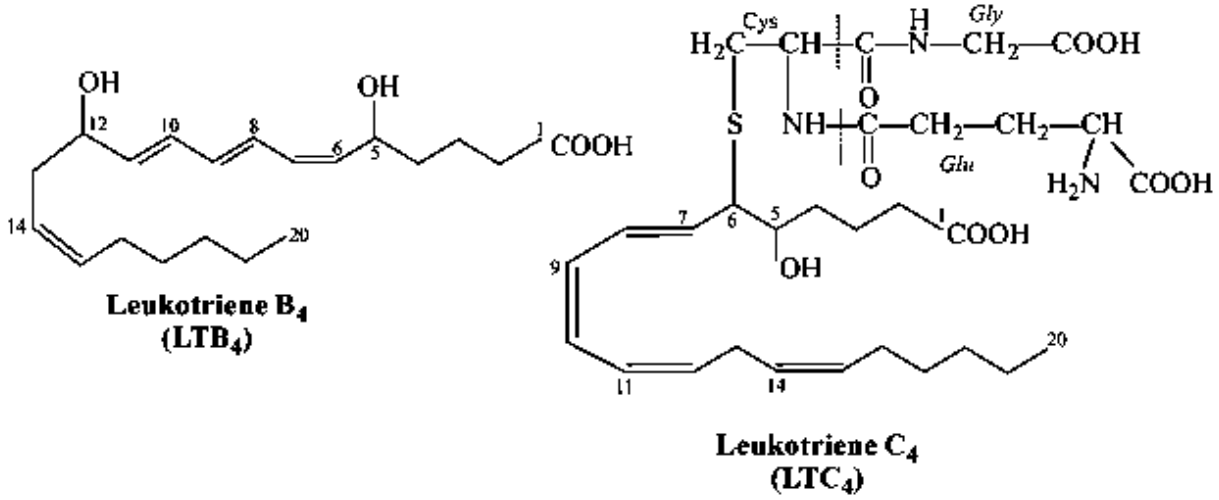


Figure 25. Leukotrienes structure

Leukotriene B4 (LTB4) has two hydroxyl groups at C-5 and C-12 and three conjugated double bonds at C-6, C-8 and C-10. An additional double bond is

present between C-14 and C-15. **Leukotriene C4** (LTC4) contains the tripeptide glutathione (γ-Glu-Gly-Cys) covalently bonded to a derivative of arachidonic acid. **Leukotriene D4** (LTD4) possesses the dipeptide, Gly-Cys (Glu residue is eliminated) and **leukotriene E4** (LTE4), the amino acid Cys (Gly residue eliminated).

Neutrophils make one class of leukotrienes to alter mobility and act as chemotactic agents. *Mast cells* make another class, formerly known as **slow-reacting substances**, which is responsible for bronchial constriction and other anaphylactic allergic reactions. Leukocytes are powerful biological signals; for example, they induce contraction of the muscle lining the airways to the lung. They also cause a slow and persistent contraction in the smooth muscle of blood vessels. Overproduction of leukotrienes causes asthmatic attacks and also stimulates mucus secretion.

B. Biosynthesis Various eicosanoids are produced in different cell types by different synthetic pathways, and have different target cells and biological activities. While prostaglandins are made everywhere in the body, synthesis of thromboxanes and leukotrienes occurs in restricted locations. Both compounds are synthesized in platelets, neutrophils and the lung. Some amount of thromboxane production also takes place in the brain. Figure 26 depicts various reactions involved in the biosynthesis of 3 types of eicosanoids from arachidonic acid.

Arachidonic acid is generated from phospholipids by the action of *phospholipase A* 2 (PLA2), or from diacylglycerol by the action of a *lipase*. The biosynthesis of most eicosanoids starts at arachidonate, which has 4 double bonds at C5, C8, C11 and C14. In the first key reaction, arachidonate gets converted to prostaglandin H2 (PGH2) by the enzyme *prostaglandin synthase*, which is made up of two components, cyclooxygenase and hydroperoxidase. This is a two-step reaction. In *first step*, cyclooxygenase component of prostaglandin synthase catalyzes the addition of one mole of oxygen to C-9 of arachidonate and of a second mole to C-15.

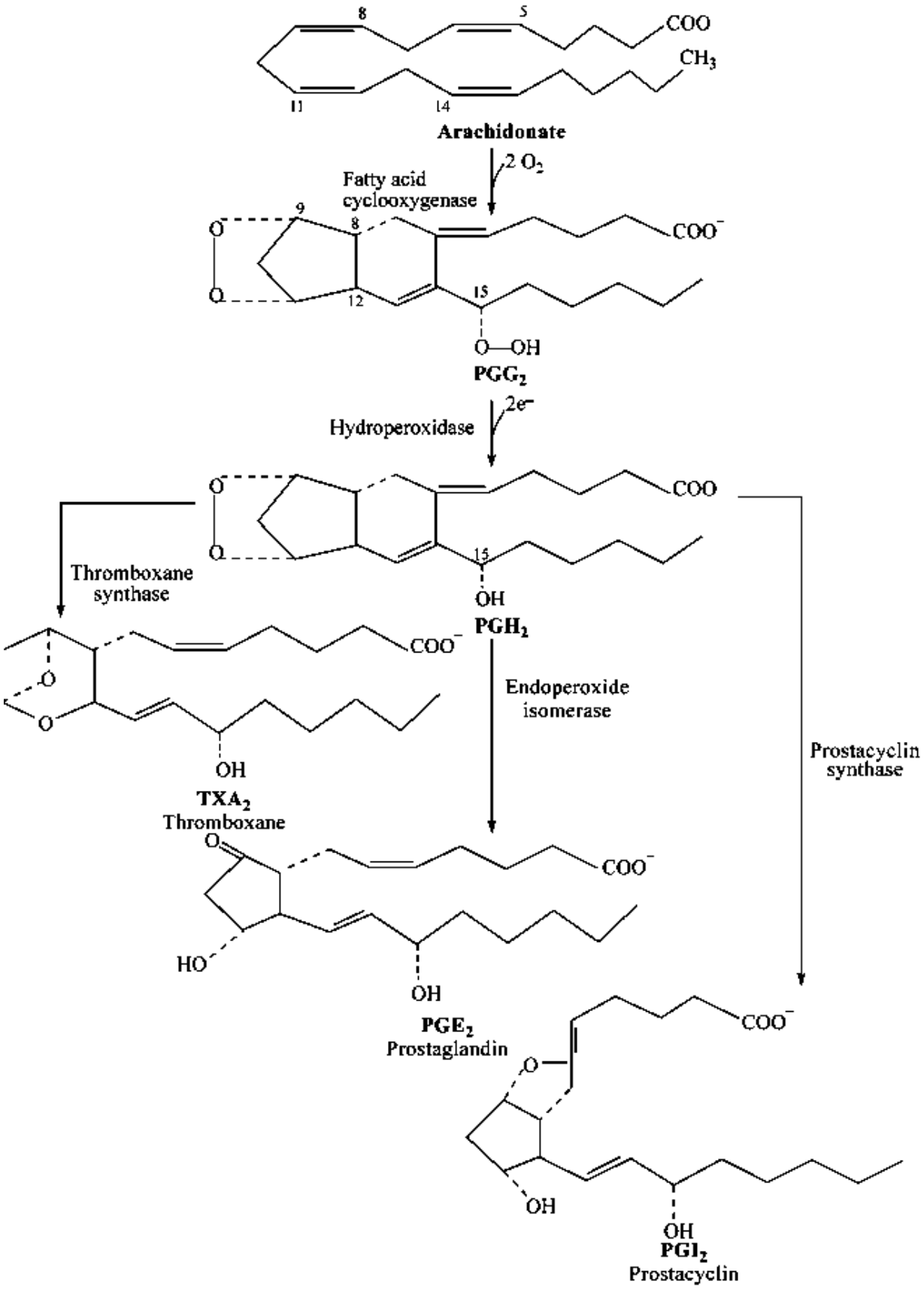


Figure 26. The biosynthesis of 3 types of eicosanoids from arachidonic acid

The bond formation between C-8 and C-12 accompanying this oxygenation produces the 5-membered endoperoxide ring structure, characteristic of eicosanoids. The compound so formed is called as **prostaglandin G2** (PGG2). The 4 oxygen atoms introduced into PGG2 come from 2 moles of oxygen. In the second step, the hydroperoxidase component of prostaglandin synthase, then, catalyzes a two-electron reduction of the 15-hydroperoxy group of PGG2 to a 15-hydroxyl group, producing **prostaglandin H2** (PGH2). The highly unstable PGH2 is rapidly transformed into other prostaglandins, prostacyclins and thromboxanes. In fact, the biochemical fate of the PGH2 synthesized is determined by tissue-specific enzymes. For example, in a tissue producing prostaglandin E2, the enzyme endoperoxide isomerase is present and converts PGH2 into **prostaglandin E2** (PGE2). The synthesis of PGE2 from arachidonate was the first-ever pathway elucidated for eicosanoid production and was discovered by Bengt Samuelsson and his associates in 1964

The wondrous drug aspirin has been used for centuries to decrease inflammation, pain and fever. Its mode of action was an enigma until John Vane, in 1975, discovered that *aspirin inhibits the synthesis of prostaglandins by inactivating prostaglandin synthase*. Specifically, aspirin (acetylsalicylate) irreversibly inhibits the cyclooxygenase activity of this enzyme by acetylating a specific serine hyydroxyl group. Aspirin is a potent antiinflammatory agent because it blocks the first step in the synthesis of prostaglandins. This drug is also widely used to prevent excessive blood clotting, which can lead to heart attacks and strokes. Aspirin is antithrombotic also because it blocks the formation of thromboxane A 2 (TXA2), a potent aggregator of blood platelets. Inhibition of the cyclooxygenase blocks the formation of prostaglandin H2, PGH2. PGH2, which is produced in the platelets, is also the precursor of thromboxane A2 (TXA2); the reaction being catalyzed by the enzyme *thromboxane synthase*. **Prostacyclin I2 (**PGI2) is synthesized from PGH2 and the reaction is mediated by *prostacyclin*

synthase. Thus, we see that the tissues are differently endowed with enzymes that transform endoperoxides into sepcific types of eicosanoids.

Leukotrienes are made from arachidonate by another pathway, beginning with the addition of oxygen to C-5 of arachidonate ; the reaction being catalyzed by *lipoxygenase*. This reaction is not affected by antiinflammatory drugs.

TESTS FOR SELF-CONTROL

1. Choose the biologically active agents that are regulators of homeostasis and are secreted by special glands:

A. Triacylglycerols

B. Vitamins

C. Enzymes

D. Hormones

E. High Fatty Acids

2. Choose the biological action that is typical for hormones, only:

A. To regulate some processes in the target cell

B. To catalyze chemical reaction

C. To be linked to the active centre of an enzyme

D. To change the pH of the environment

E. To transfer the substance across the blood stream

3. Choose the term of hormonal compounds that are secreted from hypothalamus:

A. Neurotransmitters

B. Conjugation Agents

C. Releasing factors

D. Eicosanoids

E. Antioxidants

4. Choose the department of CNS, where tropic hormones are secreted from:

A. Cerebral cortex

B. Pituitary gland

C. Hypothalamus

D. Striate body

E. Yellow spot

5. Point out the chemical nature of hormonal receptors:

A. Nucleic acids

B. Carbohydrates

C. Proteins

D. Vitamins

E. Lipids

6. Choose the name of the secondary messenger that takes part in the transmission of hormonal signal:

A. Inosine triphosphate

B. Cupper ion

C. Calcium ion

D. Transferrin

E. Cyclopentano perhydrophenanthrene

7. Point out the function for alpha-subunit of G-protein formed after dissociation of Gs protein:

A. The receptor to hormone

B. The energy source for target cell

C. The stimulator of adenylate cyclase

D. The inductor of transcription

E. The protein channel in the cellular membrane

8. Find out the tropic hormone whose secretion will be suppressed under excess glucocorticoid levels in the blood:

A. STH

B. ACTH

C. FSH

D. SIH

E. LH

9. Point out the location of insulin receptor in its target cell:

A. Nucleus

B. Cytoplasm

C. Mitochondria

D. Cellular membrane

E. EPR smooth part

10. Point out the product of Adenylate cyclase reaction:

A. cGMP

B. Protein kinase A

C. cAMP

D. Diacylglycerol

E. Inositol 1, 4, 5 -triphosphate

11. Point out the location of the receptor for steroid hormone in a target cell:

A. Membrane

B. Mitochondria

C. Ribosome

D. Cytoplasm

E. Lysosome

12. Point out the hormone that is intermediate metabolite for testosterone and estradiol synthesis:

A. Aldosterone

B. Cortisol

C. Progesterone

D. 25-hydrooxy cholecalciferol

E. 17-ketosteroid

13. Point out the major hormone of luteal phase in females:

A. Progesterone

B. Cortisol

C. Aldosterone

D. Androstenedione

E. 17-ketosteroid

14. Find out the substance whose content will be increased in the blood after the influence of glucocorticoids on the liver metabolic pathways:

A. Glucose

B. Alanine

C. Palmitic acid

D. Oxygen

E. Carbon monoxide

15. What function in the target cell may be found for thyroxin at its levels which are higher then physiological?:

A. Catalytic function

B. Secondary messenger function

C. Uncoupler for oxidative phosphorylation

D. Allosteric inhibitor for ATP synthetase

E. Suppresser of calcium transport across cellular membrane

16. What amino acid residue is considered as precursor for thyroid gland hormone formation:

A. Glycine

B. Alanine

C. Proline

D. Tyrosine

E. Valine

17. Find out the main target tissues for parathyroid hormone (PTH):

A. Liver tissue, only

B. Bone, kidney tissues

C. Nervous tissue

D. Spleen tissue

E. Skeletal muscular tissue

18. Name the index of blood plasma whose content will be increased after parathyroid hormone secretion:

A. Calcium ions

B. Ammonia

C. Urea

D. Uric acid

E. Zinc ions content

19. Name the enzyme whose activity is controlled by PTH in kidney tissue:

A. Alpha-1-hydroxylase

B. 25-hydroxylase

C. Pyruvate dehydrogenase

D. Prostaglandin synthetase

E. Prostacyclin hydratase

20. What influence of calcitriol on kidney tissue is observed at its excess levels in the blood?

A. Protein degradation induction

B. The feed-back inhibition of alpha-1-hydroxylase

C. The allosteric activation of alpha-1-hydroxylase

D. Activation of calcidiol formation

E. Inhibition of calcidiol formation

21. Name the index of blood plasma whose content will be increased after TSH secretion:

A. Calcium ions

B. Ammonia

C. Thyroxin

D. Uric acid

E. Cortisol

22. What influence on anterior lobe of pituitary gland is found for somatostatin?

A. Protein degradation induction

B. The feed-back inhibition of all tropic hormones secretion

C. The suppression of growth hormone (GH) secretion, only

D. The suppression of GH, TSH secretion

E. Calcium mineralization stimulation

23. What factor can decrease the ACTH secretion by anterior lobe of pituitary gland:

A. Excess levels of glucocorticoids in the blood

B. Melanoliberin

C. Corticoliberin

D. Excess Calcium levels in the blood

E. Low levels of glucose in the blood

24. Find out the condition for glucagon secretion:

A. High levels of calcium in the blood

B. Low levels of glucose in the blood

C. High levels of glucose in the blood

D. High levels of cholesterol in the blood

E. Low levels of cholesterol in the blood

25. Find out the ions content whose levels in the blood plasma is regulated by aldosterone :

A. Calcium ions

B. Copper ions

C. Iron ions

D. Sodium ions

E. Phosphate ions

26. Point out the hormone that can stimulate lipogenesis in adipose tissue at hyperglycemia state:

A. Insulin

B. Aldosterone

C. Glucagon

D. Thyroxin

E. Prostacyclin

27. Name the hormone whose function is to suppress the cholesterol synthesis in the liver:

A. Growth hormone

B. Aldosterone

C. Glucagon

D. Thyroxin

E. Prostacyclin

28. Find out the eicosanoid that stimulates the aggregation of platelets in the blood stream:

A. Prostaglandin H

B. Leukotriene

C. Ceruloplasmin

D. Thromboxane A2

E. Prostacyclin

29. Find out the key enzyme for all Prostanoids formation in humans:

A. Cyclooxygenase

B. Prostaglandin isomerase

C. Transferase

D. Monoamino oxidase

E. Hemoglobin oxygenase

30. Name the drug whose function is to inhibit the cyclooxygenase of arachidonic acid in human tissues:

A. Vicasol

B. Leukomycin

C. Indometacin

D. Cortisol

E. Hydrocortizone

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Розглянуто і затверджено на засіданні циклової методичної комісії хімічних дисциплін Запорізького державного медичного університету (протокол №_____ від_____ 2016 року)