BIOCHEMISTRY OF HORMONES

Thyroid hormone

Thyroid hormone: the thyroid gland has two active hormones namely T_4 (Tetra-ido-thyronine) and T_3 (Tri- ido-thyronine)

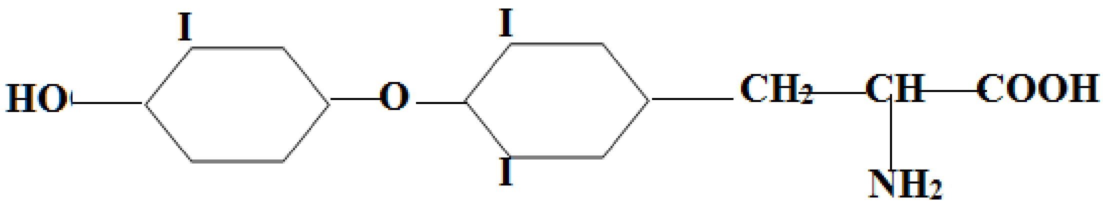


Fig. 3,5,3`- Tri-ido-thyronine (T_3)

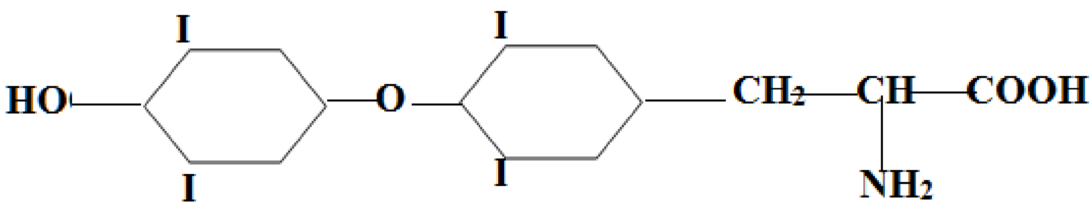


Fig. 3,5,3`,5`- Tri-ido-thyronine (T_3)

Synthesis and release of thyroxine

Iodide is actively transported from blood to thyroid follicular cells by sodium potassium symporter. The Iodide "I^- is converted to Iodide free radical "I*" catalyzed by peroxidase. The free radical I* instantaneously binds to phenyl group of tyrosine to form mono-iodo-tyrosine (MIT). The MIT then converts to Di-iodo-tyrosine (DIT).
Two molecules of DIT are combined to form T_4 and one molecule of MIT and one molecule of DIT are combined to form T_3.
These iodination reactions can be blocked by

- Sulfa drugs.
- Thioureas.
- Para-amino-benzoic acid (PABA).

Storage of hormone

The iodinated thyroglobulin is stored in the lumen of the follicles.

Release of hormone

The thyroxine is released by thyroid stimulating hormones. The T_3 and T_4 are released into blood circulation. The tyroxine that is present in blood is 90% T_4 and 10% T_3.

In blood the hormone is carried by thyroxine binding globulin (TBG). The TBG is absent in cats, rabbits, rats, mouse, guinea pigs, pigeons and chickens. In these species the thyroxine binds to blood albumin.

Action of thyroid hormone:

1. Increases temperature and heart function.
2. Increases oxygen consumption (increases BMR).
3. Increases glucose turnover and absorption.
4. Decreases blood cholesterol level.
5. Stimulation of growth and maturation.
6. Stimulates erythropoiesis.
7. Stimulates protein synthesis.

Molecular basis of action of T_3 or T_4.

1. Action of T_4: Under normal condition 3 moles of ATP are synthesized per atom of oxygen (1/2 O_2) thus the P:O ratio equals to 3. The system is said to be uncoupled if P:O ratio is less than 3.
   The thyroid hormone lowers the P:O ratio by uncoupling. So more amount oxygen consumption takes place and large amount of oxidative energy not incorporated into ATP is lost as heat.
2. T_3 stimulate protein synthesis.
3. T_3/T_4 stimulates Sodium-potassium pump at the cell membrane.

Parathyroid hormone

The ratio of Ca to phosphate in blood is approximately 3:2. Roughly 50% of Ca is blood is bound mostly to albumin and other 50% as ionized form (Ca^{2+}). The bones are both, the source of blood calcium during hypocalcemia and a place for the storage of Ca during hypercalcemia.

The phosphates are widely distributed in soft tissues as phospholipids, DNA, RNA, Glycogen, ATPs etc. The phosphates exists in blood exclusively as free ion. The blood calcium is regulated by three hormones namely parathyroid hormone (PTH), Calcitriol or 1,25-dihydroxy cholecalciferol, calcitonin.

Action of PTH on bone

PTH is 84 amino acid polypeptide hormone synthesized by cheif cells of parathyroid gland. Activate osteoclasts to break down bone tissues to release calcium in blood. The effects of PTH induced osteolysis are

1. Release of lysozomal enzymes – Hydroxylases, colagenases.
2. Activation of acid phosphatise and carbonic anhydrase.
3. Activation of the proton pump (H/K^+ ATPase).
4. Accumulation of lactate and citrate.
5. Increased synthesis of hyaluronate and sulphated mucopolysacharide.

All these contribute to provide enzymes to breakdown bone matrix causing dissolution of calcium salts and allow a suitable acidic pH for bone break down with a restricted area under the osteoclast.

Action of PTH on kidney tubules

PTH activates adenylyl cyclise that elevates the intracellular level of cyclic AMP (cAMP) that stimulates a cascade of reaction that enhances the tubular absorption of calcium.

PTH action of Vitamin D

The PTH causes activation of Vitamin D. The Vitamin D facilitates the absorption of calcium from duodenum and phosphates from jejunum.

Calcitonin

Calcitonin is 32 amino acid polypeptide hormone secreted by C-cells. The principal role of calcitonin is lowering of blood calcium. The osteoclasts have one million high affinity receptors for calcitonin per osteoclast cells.

Principal functions of calcitonin:

1. Inhibit bone resorption by osteoclast cells.
2. Increases calcium excretion in urine.

Insulin

Produced by Beta cells of pancrease. After production of the hormone it is stored in secretory granules of Beta cells. The release of insulin is stimulated by glu7cose, amino acids, Hormones (glucogon, gastrin, secretin, pancreozymin) and drugs such as sulfonyl ureal, isoproterinol).

The hormone is inhibited by hypoglycemima, somatostatin and drugs such as phenothiazines.

Site of insulin degradation:

Primary site: Liver.

Secondary site: Kidney.

The major roles of insulin in glucose metabolism:

1. Glucose transport across the membrane of muscle and fat cells.
2. Glucose utilization by increasing enzyme catalyzed reaction in liver cells.

Effect of insulin on liver:

1. Stimulates glucose oxidation.
2. Stimulates glycogen synthesis.
3. Stimulates lipid synthesis.
4. Stimulates protein synthesis.

Muscle (Skeletal and Cardiac):

1. Stimulates glucose uptake.
2. Stimulates Glycogen synthesis.
3. Stimulates glucose oxidation.
4. Stimulates amino acid uptake by muscle cells.
5. Stimulates uptake of K^+ ions by muscle cells.
6. Stimulates protein synthesis.

Role of insulin in adipose tissues:

1. Stimulates glucose uptake.
2. Stimulates glucose oxidation.
3. Stimulates lipid synthesis.
4. Stimulates uptake of K^+ ions by adipose cells.

As a whole effect of insulin on the whole animal is

- Increase in anabolism, food intake and respiratory quotient.

Insulin binds to the insulin receptors and activates glucose transporters (GLUT-4) causing the entry of glucose and fats in the cells.

Glucagon

It is a polypeptide hormone secreted by alpha cells of islets. The release of this hormone is stimulated by hypoglycaemia.
Action of glucagon on liver:
It acts on liver and stimulates gluconeogenesis and glycogenolysis increasing blood glucose level. The glucagon binds to cell surface receptors (hepatocytes). The receptors then activated adenylyl cyclase which in turn converts ATP into cAMP. The cAMP activates protein kinase that menifests various biochemical effects of glucagon.
Action of glucagon on Adipose tissues:
Stimulates lipolysis causing release of free fatty acids into blood circulation.

Mineralocorticoids

Secreted by zona glomerelusa cells of adrenal cortex. The principal mineralocorticoid is aldesterone. It acts on renal tubules.
Principal functions:

1. Aldesterone stimulates reabsorption of sodium causing increase in ECF volume (Extra-cellular fluid).
2. Aldesterone stimulates urinary excretion of potassium and H^+ uibs.
3. Aldesterone promotes excretion of Mg^{2+} and NH_4^+ (Amonium ions).

Regulation of Mineralocorticoid Secretion

The regulation of mineralocorticoids is pituitary independent (unlike that of gluco-corticoids).
The low ECF volume and hyponatrimia (lower sodium concentration in blood) stimulates the secretion of proteolytic enzyme Renin from renal Juxta Glomerular apparatus. Renin acts on circulating protein Angiotensinogen (produced from liver) converting it to active form called Angiontensin-I. Angiotensin I gets converted to Angiotensin II in lungs. The Angiotensin II stimulates aldesterone secretion by Zona Glomerulosa in adrenal cortex.

Testosterone

This homone is steroid hormone that is derived from cholesterol. This hormone is basically needed for spermatogenesis.
The Leidig cells of testis contain an enzyme called 18-hydroxylase that converts cholesterol into Testosterone that is subsequently converted to Dihydro-Testosterone.

Cholesterol
↓ 18-hydroxylase
Testosterone
↓
DihydroTestoster

The pig testis porduces another hormone that is a pheromone called *androstenone*. This hormone is secreted through saliva that gives boar tint of fat and muscle of adult boar. This gives an unpleasent smell to meat. Thus it is customary to castrate the male pigs intended for meat production. The castration stops the androstenone production and reduces skatole production (the boar tint is produced by combination of androstenone and skatole produced by bacteria of large intestine). The androstenone inhibits the enzyme that is required for degradation of skatole.

Regulation of testosterone

Leutinizing hormone (LH) binds to LH-receptors in Leidig cells. This stimulates the production of cAMP. The cAMP in turn activates Protein Kinase A. The Protein Kinase A activates the enzyme 18-hydroxylase that converts the cholesterol to testosterone.
The testosterone is released to plasma with being bound to testosterone binding protein. About 2% of the testosterone is not bound to testosterone binding protein. This free form of testosterone is active form of circulating testosterone.
The testosterone inhibits the secretion of GnRH from hypothalamus and inhibits LH secretion (negative feedback mechanism).

Biological effects of testosterone

1. Development of male sex organs during foetal life.
2. Growth of male sex organs and accessory sex glands arround the time of puberty mainly by dihydro-testosterone.
3. Testosterone stimulates growth of the skeleton and skeletal muscle in the male. The testosterone stimulates the protein synthesis and inhibits the protein breakdown thus castrated male animals have more fat and less muscle mass.

The small amount of testosterone produced by Leidig cells are taken up by Sertoli cells. The testosterone taken up by Sertoli cells are converted to estradiol. Dogs with Sertoli cell tumor develope feminization.

Estrogen

Estrogen is C_{18} steroid compound. Chemically it is 17-β-estradiol.

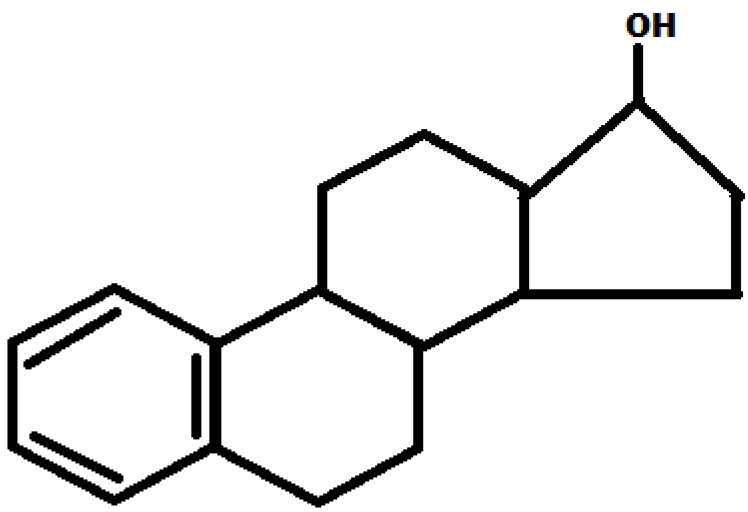
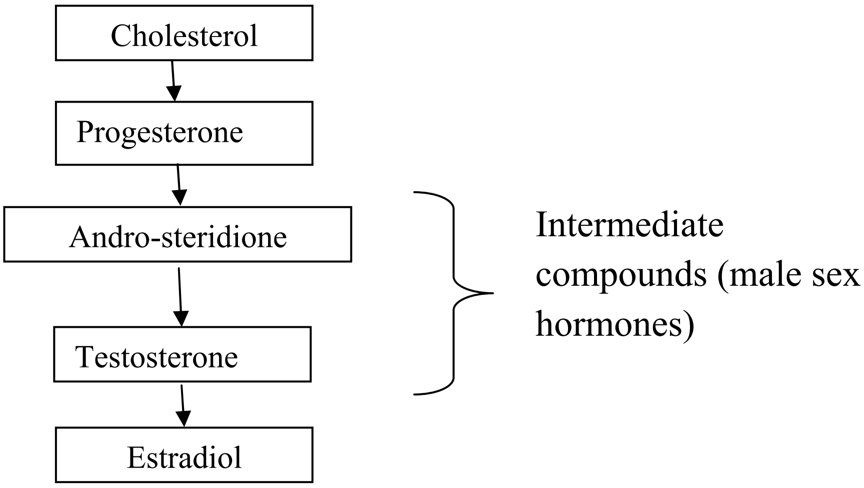


Fig. Structure of 17-β-estradiol.

Several plant and fungi also produce compound that have estrogenic properties called Phytoestrogens.
Site of synthesis of estrogen: Ovary, Placenta, Adrenal Cortex, Sertoli cells of Testes.
In blood, 98% of the estrogen is bound to transport protein when present in blood.

<u>Biosynthesis of estrogen starts from cholesterol</u>



<u>Effects of estrogen</u>
1. Stimulates follicular growth and signal follicular maturation.
2. Affects the female sexual behavior.
3. Helps in the transport of spermatozoa.
4. Growth and development of mamary tissues.
5. Contribute to preparation of the uterus for parturition.

Progesterone

Produced in the corpus luteum and its primary function is to create favorable conditions for the growth adn development of fetus and neonate.
The synthesis of progesterone is stimulated by LH.
<u>Effects of progesterone</u>
1. Create the conditions in the lungs favorable for the development of embryo.
2. Prevents the development of follicles and new ovulation.
3. Stimulates the growth and development of the uterus during pregnancy.
4. Contribute to growth and development of mammary tissues and prepare for milk synthesis.

Progesterone increases growth of the glands in endometrium. This stimulates their secretion of mucin, carbohydrates, specific proteins for nourishment of embryo before implantation.
Progesterone stabilizes the myometrium, preventing contration of it that could lead to premature birth.
Like estradiol, 98% of the progesterone is bound to transport protein when present in blood.

Growth Hormone (GH)

The primary action of Growth Hormone is growth of body mass and elongation of bones.
Site of synthesis: somatopropes (Anterior pitutary).

<u>Regulation of secretion:</u>
GH secretion is stimulated by GH-RH (Growth Hormone Releasing Hormone) and is inhibited by GH-IH (Growth Hormone Inhibitory Hormone) that is also called somatostatin.
<u>Factors increasing GH secretion:</u>

1. Physical exertion.
2. Fasting.
3. Stress.
4. Protein rich feed.
5. Low glucose concentration.

<u>Hormonal regulation of GH:</u>
GH secretion is stimulated by thyroid hormone and sex hormones.

<u>Effects of GH</u>

1. Stimulates differentiation of chondrocytes.
2. Stimulates production of IGF-1 (insulin like growth factor or pro-insulin).
3. Stimulates protein synthesis.
4. Stimulates lipolysis.
5. Stimulates glucose production.
6. Reduces glucose utilization.

} Increased blood glucose

IGF-1 helps in augmenting the growth stimulating action of GH

Posterior Pitutary Hormones

Site of production: Neuroendocrine cells of hypothalamus.
Site of secretion: Nerve ending at posterior pitutary gland.
The neuroendocrine cells produce these posterior pitutary hormones and package them in vessicles. Then these are transported along the axons to posterior pitutary gland and stored inside the vessicles in the nerve endings.
The two peptide hormones secreted by posterior pitutary gland are:

1. Anti-diuretic hormone (ADH) (also called vassopressin).
2. Oxytocin.

ADH and Oxytocine are peptide hormone made of 9 amino acids.

Anti-diuretic hormone (ADH)

Site of action: kidney.

<u>Mechanism of action of ADH:</u>

This hormone regulates water permiability of renal distal tubules and renal collecting ducts by regulating density of water channels called aquapores. ADH increases the aquapores which aid in reabsorption of water in kindney tubules. As a result of increased aquapores there is increase in water reabsorption causing decrease in osmolarity of ECF (Extra-cellular fluid). This leads to increase in urinary solute concentration and decrease in urinary volume (because less amount of water is being excreted through urine).
Regulation of ADH secretion:

- Decrease in osmolarity of ECF (Extra-cellular fluid) leads to decrease in ADH secretion.

- Increase in osmolarity of ECF (Extra-cellular fluid) leads to increase in ADH secretion.

The extracellular fluid volume decreases in conditions of water loss from the body such as diarrhea and vomiting.

Oxytocin

Site of action: smooth muscle cells of uterus and alveolar ducts of mamary glands.
In uterus oxytocin causes the contration of uterine smooth muscle causing the uterine contration that is helpful during parturition.
In alveolar ducts of mammary glands, the oxytocin generates pressure in mammary glands that drives the milk to large excretory ducts and teats.