HORMONES

Definition

Hormones are chemical messengers secreted into blood by endocrine or ductless glands.

However many hormones are secreted by organs which are not ductless glands. Hormone means to arouse or to excite.

Major endocrine glands are pituitary, hypothalamus, thyroid; adrenals, pancreas, ovaries and testes. Others are Thymus, Pineal gland and gastro intestinal hormones.

Hormones can be classified based on their structure, mechanism of action, based on their site of production etc.

Hormones reach target organs, exert their metabolic effects, also reach their site of production. Here, they inhibit the production of the hormone. This is called as feed back inhibition. Sometimes the concentration of the hormone is less, which stimulates the production of hormone by a process of feedback stimulation

Biosynthesis of Hormones

Biosynthetic mechanisms are many. Some protein hormones are synthesized as precursors, which are converted to active form by removal of certain peptide sequences. E.g. Insulin is synthesized as pre-proinsulin (m.wt11500).Removal of some amino acids, peptides Producer insulin. Thyroxine, a single amino acid hormone. It is synthesized as a glycoprotein precursor called thyroglobulin, which has 115 amino acids. Other hormones like glucocorticoids/ minerolacorticoids from Adrenal gland are synthesized and secreted in their final active form. **Pro-hormones:** Some hormones are synthesized as biologically inactive or less active molecules called pro-hormones. Usually they are polypeptides/ proteins. Eg.Pre-proinsulin→Proinsulin.

Storage

Hormones are stored in secretory granules within the cytoplasm of endocrine cells. eg. Thyroid hormones are stored in follicles filled with colloid particles. Catechoamines of Adrenal medulla are stored in secretory granules of cytoplasm.

- Storage always protects the molecule from untimely inactivation.
- Steroid hormones are not stored in significant quantities.
- In response to stimulus they are synthesized and released immediately.

Release:

• When the target cells require free hormones, they are released immediately.

• The deficit in the bound form is replaced by the secretion of the endocrine gland. Feed back inhibition/stimulation controls hormone release .

• Protein, polypeptide hormones are released by exocytosis or pinocytosis. It involves fusion of granules and cellular membrane, followed by secretion in to blood stream.

• Stimulus excites the endocrine cell.

• The specific enzymes in the storage vesicle activate the hormone before release.

• Disruption of the process by certain drugs interferes with exocytosis.

• The secretory process is linked to the release of neurotransmitters.

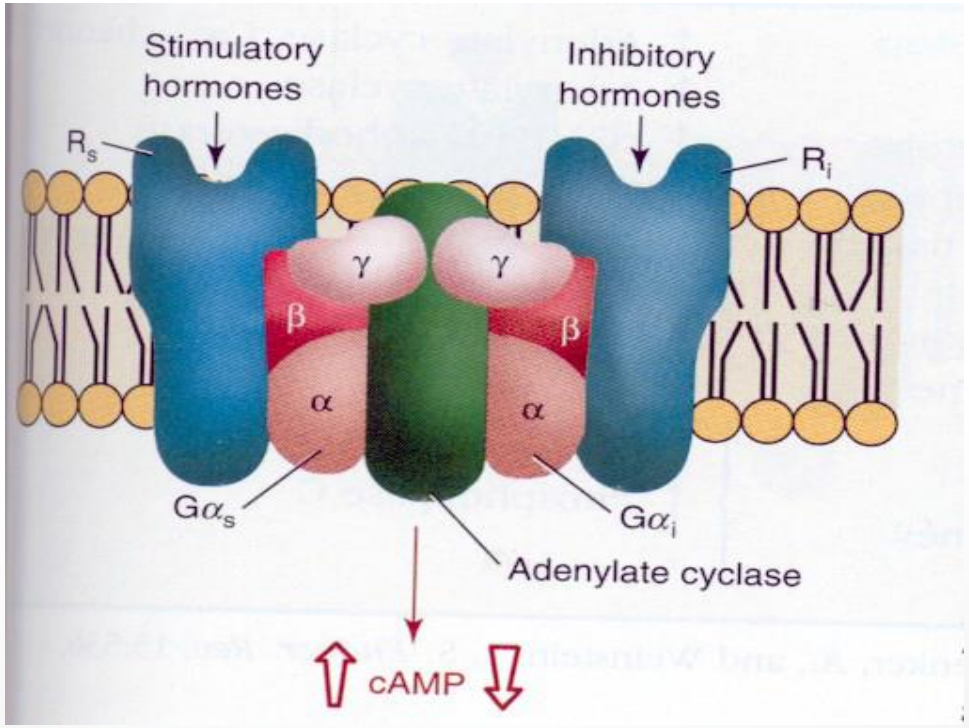
Binding of hormone to receptor leads to:

• Conformational change in the receptor and G-protein (α, β, γ subunits).

• It cleaves the trimeric form into activated α-GTP complex.

• G-protein is a peripheral protein; which diffuses along the inner surface of the plasma membrane to reach the effector protein.

• Through allosteric modification the message is conveyed to the effector protein.



Receptors

Receptors: are molecules which recognize specific hormone.

Cell surface contains receptors for the peptide, protein, glycoprotein hormones.

Lipophilic hormones like steroids, thyroxine are recognized by intracellular receptors, eg. Steroid receptor is in cytoplasm. It is a soluble oliomeric protein found in cytoplasm or nucleus.

Thyroxine receptor is in nucleus (HRE). Lipid soluble hormones cross the cell membrane easily. Receptor binding to hormone involves electrostatic and hydrophobic interactions, and is usually reversible process. Binding influences effector molecule, cause several other molecular events.

Cytosolic receptors found for the following.
a. Glucocorticoids. b. Mineralocorticoids c. Progestins.
d. Estrogens. e. Calcitriol.

Nuclear receptors are identified for Thyroxine, Triiodothyronine

Cell surface receptors with second messenger as c-AMP found for the following hormones:

ADH, HCG, LH, FSH, TSH, MSH, ACTH, CRH, Calcitonin,, Glucagon . Parathyroid hormone, somatostatin, angiotensin.

Regulation of receptors:

There are number of specific receptors in the target cells.. There are two mechanisms for regulation.

1- Down regulation: There is internal distribution of receptors such that few receptors are ava Prolonged exposure to high concentration of hormone leads to decreased receptors, called as desensitizationilable on the cell surface. This leads to decreased response in target tissue. More receptors reach cell membrane when the hormone concentration is low. Removal of receptor to the interior or cycling of membrane components alters the responsiveness to the hormone.eg. Insulin receptors can be shuttled تنتقل between cytoplasm and cell membrane. In another type of down regulation, H-R complex, after reaching nucleus controls the synthesis of receptor molecule.

Some times Covalent modification of receptors by phosphorylation decreases binding to hormone, which diminishes signal transduction.

2-Up regulation*:* Some hormones like prolactin up regulate,(increase) their own receptors which ultimately increases the biological response and sensitivity in target tissues.

Second messengers:

Second messengers: calcium, phosphatidyl inositiols are identified for GnRH, TRH, Acetyl choline, Angiotensin-II, Vasopressin. Insulin, GH, Prolactin, Oxytocin have unknown intracellular messengers.

Hormone itself is first messenger. The message is communicated to the cell Via Second messengers.

1. **Cyclic AMP as second messenger**: ATP is converted to cAMP by the effector protein, adenyl cyclase. This enzyme is activated when hormone binds to receptors. The signal is transmitted through G protein called Gs. It is a trimer consisting of α, β and γ subunits. When H binds to receptor, there is GTP induced dissociation of the subunits, GTP binds to α- subunit.

2. Calcium, as second messenger: Hormones exert their action via Ca, PI, or both. Intracellular Ca is increased by:

a) Entry of Ca from extra cellular region when stimulated.

b) Inhibition of Ca pumps, which pumps out Ca ions in exchange for H ions. c) Release of Ca ions from intracellular reseveroirs like mitochondria, endoplasmic reticulum.

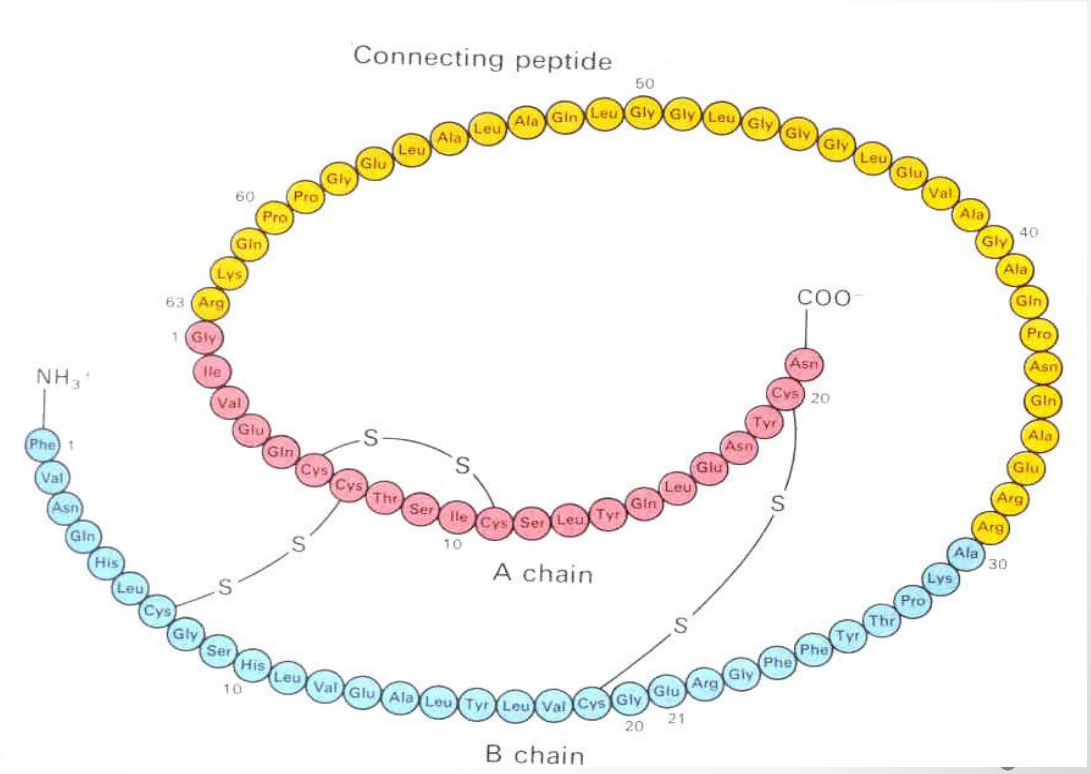
3. Phosphatidyl inositol 4, 5 bisphosphate. Binding of hormone to receptor results in the cleavage of phosphatidyl inositol by phospholipase-c (PLC) to diacyl glycerol(DAG) and Inositol- 1, 4, 5, triphosphate (IP_3).Intracellular IP_3 releases Ca ions. A calcium binding protein, calmodulin binds Ca .

4**. Diacyl glycerol (DAG)**, activates Ca-phospholipids dependent protein kinase which in turn phosphorylates several intracellular proteins. P KC has regulatory and catalytic domain. In the absence of DAG, Ca and phospholipids, there is interaction between regulatory and catalytic sites. This results in inactivation of the enzyme.

INSULIN

Insulin is a protein hormone secreted by β-cells of Islets of Langerhans of pancreas.

Chemistry: It is composed of 2 polypeptide chains, A and B, containing total of 51 amino acids. A chain has 21 and B has 30 amino acids. The two chains are held together by disulfide linkages. If the disulfide bonds are broken the insulin molecule is inactivated.



Biosynthesis of Insulin

Pre-pro insulin (109 amino acids) is synthesized in the endoplasmic reticulum of B Cells of islet of Langerhans. It is acted up on signal peptidase, gets converted to proinsulin (86AA). It is transported to Golgi where it is hydrolyzed to insulin (51AA) by trypsin like protease and carboxy peptidase B. The process liberates inactive C-peptide of 31a.a and 4 other amino acids from the C-terminal. C-peptide determination in urine is related to the insulin out put from pancreas. It is used to differentiate endogenous to exogenous source of insulin.

Condensing vacuoles are pinched off from Golgi cisternae with equal quantities of insulin and C peptide. Insulin is secreted via exocytosis. Insulin is biologically active, pro insulin is inactive.

Catabolism: Plasma half life of insulin is 3 to 5 minutes. It is catabolised in liver, kidney and placenta.

a. Liver, kidney contains protease which is specific for insulin degradation.

b. Insulinase or Glutathione-insulin trans hydrogenase is located in liver, kidney, muscles and placenta. It causes reductive cleavage of S-S bonds.

c. After the reductive cleavage, the A&B chains are hydrolyzed by proteolysis. Mechanism of insulin action. When insulin binds to specific receptor, several events take place.

A. There is conformational change of the receptor.

B. The receptors crosslink and form micro aggregates.

C. The receptor complex is internalized.

D. One or more signals are generated; however the role of second messenger is uncertain

Regulation of Insulin Receptors

High levels of insulin in blood decrease the insulin receptors on the target membrane. Here insulin-receptor complex is internalized, there by causing less sensitivity of target tissue.

Regulation of Insulin secretion:

Secretion of insulin is closely coordinated with the release by pancreatic α- cells. Insulin along with glucagon maintains glucose levels.

A- Insulin secretion is increased by increase in glucose. B-cells of pancreas have sensors to glucose. High levels of glucose stimulate insulin secretion and decrease glucagon release.

B- High levels of amino acids in the plasma induce the secretion of insulin.

C- Gastrointestinal hormones like secretin and others are released in response to intake of food.

They induce anticipatory secretion of insulin, before the rise of glucose in the portal vein. Therefore when glucose is given orally it induces more insulin secretion than when given intravenously.

d. Glucose stimulates secretion of insulin and inhibits the release of glucagon.

e. Synthesis, release of insulin is decreased when there is scarcity of dietary fuels.

Metabolic Role of Insulin

Carbohydrate metabolism: Insulin produces lowering of blood glucose and increases glycogen stores. This is achieved at several metabolic stages. *There is increased uptake of glucose, galactose by various tissues like muscles, adipose, mammary glands etc .It is due to increased translocation of glucose transporters from Golgi to plasma membrane.

* Insulin induces the synthesis of glucokinase which phosphorylates and decreases the intracellular glucose in liver.

* Insulin enhances glycolysis by inducing the synthesis of phosphofructokinse and pyruvate kinase.

* Pyruvate dehydrogenase complex is activated via dephosphorylation of enzyme molecules which lead to increased production of acetyl- CoA from pyruvate. * Insulin stimulates protein phosphatase-1 which dephosphorylates and activates key enzyme glycogen synthase. This leads to increased synthesis of glycogen.

Lipid metabolism:

Insulin causes lowering of free fatty acids level in blood and increases the stores of triacylglycerol.

- **It decreases lipolysis by inactivating triacylglycerol lipase by dephosphorylation.**
- **It increases fatty synthesis by making available acetyl - CoA, and acetyl - CoA carboxylase.**
- **Triacylglycerol synthesis in the adipose tissue is increased by providing more of α- glycerophosphate from glycolysis. It also induces the synthesis of lipoprotein lipase which releases more fatty acids from the circulating lipoproteins. This provides more acyl- CoA for TG synthesis.**

Protein Metabolism:

Insulin promotes protein synthesis by:

- **Increased uptake of amino acids through increased synthesis of amino acid transporters in the membrane.**
- **Insulin effects gene transcription by increased levels of aminoacids, regulates m-RNA synthesis and also translation.**

- **It increases the enzyme ornithine carboxylase thereby increases polyamine synthesis which is required for r-RNA synthesis.**
- **Insulin modulates ribosomal activity via phosphorylation of 6s-ribosome of 40s ribosome**

Growth & cell replication:

Insulin stimulates growth in vivo, It activates fibroblast growth factor (FGF), platelet derived growth factor (PDGF) and epidermal growth factor (EGF). net effect is cell proliferation and growth is seen in liver, mammary, adrenal tissue.

Diabetes mellitus:

β-cells of islets of Langerhans fail to secrete adequate amounts of insulin or producing absolute or relatively low amounts of insulin. This causes hyperglycemia and glycosuria. The condition may be inherited as **autosomal recessive trait.صفة متنحية وراثياً**

It is a chronic disease of impaired carbohydrate metabolism. It is caused due to diminished effectiveness or deficiency of insulin. Secondary changes in the protein, lipid, water and electrolytes metabolism may also occur.

Diabetes mellitus (DM) is found usually after the age of 40 yrs. There are 22 clinical types of the disease.

Primary is of two clinical types:

Types of Diabetes:

Juvenile onset diabetes (Insulin dependent DM) Type-I, DDM.	Maturity onset diabetes. Non Insulin Dependent DM Type-II, NIDDM.
1. Less common	More common.
2. Starts around 15 yrs of age	Starts after 40 yrs of age.
3. Onset sudden and rapid	Slow and progressive.
4. Usually patients are thin, less body weight.	Associated with obesity
5. Progress is rapid, leads to ketosis.	Ketosis is rare.
6. Deficient in insulin. Initially patients Produce more insulin than normal Soon the β-cells gets exhausted, and atrophied and produce no insulin.	B-cells respond normally however there is Relative deficiency of insulin- due to insulin antagonism.
7. Plasma insulin is almost absent,	Plasma insulin levels may be- raised or normal
8. Insulin therapy is necessary.	Oral hypoglycemic agents and Dietary control is useful to the

Chronic complications of diabetes:

- Uncontrolled diabetic patients develop cataract. It is related to hyper glycemia. There is glycosylation of lense proteins or Glucose gets metabolized to sorbitol in the lense.The associated osmotic changes ultimately result in fibrosis and cataract formation.
- Diabetic damage of kidney is called diabetic nephropathy. It manifests initially as proteinuria, subsequently renal failure.
- Neurological complications like itching, neurodermatitis is common.

Hyper-insulinism

It means increased insulin production. Usually it is due to adenoma of islets of Langerhans. Occasionally they become malignant and metastasize all over the body. There is tremendous production of insulin. Since hypoglycemia is a serious possibility in these patients, they are protected by giving orally more than 1000gms of glucose/day.

Glucagon

It is produced by α-cells of islets of Langerhans of pancreas. It is also called as hyperglycemic glycogenolytic factor (HGF).It acts as a hormone and is required to mobilize metabolic substrates from the storage depots.

Chemistry: It is a polypeptide with 29 aminoacids. There are 15 different amino acids in the molecule.Histidine at N-terminal, Threonine at C-terminal end.

Synthesis: It is synthesized as pro-glucagon in α-cells. Carboxy peptidase B, trypsin like peptidase in the lysosomes of α-cells, hydrolyze it to produce active glucagon and some inactive peptides.

Role of glucagon:

* Carbohydrate metabolism:
* It increases glucose by Glycogenolysis in liver. It has no effect on muscle due to the absence of receptor. It induces synthesis of glucose-6 phosphatase.
* It increases gluconeogenesis in liver by inducing the synthesis of key enzymes. Enzymes like PEP carboxy kinase, pyruvate carboxylase, F-1, 6-bisphosphatase are synthesized to promote gluconeogenesis.
* The hormone promotes protein break down in liver to supply glucogenic amino acids.

Lipid metabolism: It promotes lipolysis of Triacyl glycerol in liver.

* Promotes β- oxidation of Fatty acids in adipose tissue.
* It decreases fatty acid synthesis by inactivating acetyl - CoA carboxylase.

Protein metabolism:

* It depresses protein synthesis.
* It promotes breakdown of proteins in liver.

Effect on mineral metabolism:

- It increases potassium, and calcitonin release which in turn causes calcium lowering effect.

Clinical aspects.

* Glucagon is used in the treatment of insulin induced hypoglycemia.
* Long acting Zn-glucagon is used in inoperable tumors of pancreas.
* It is used in acute pancreatitis for, it inhibits excessive secretion of pancreas.

Thyroxine

Follicular cells of thyroid produce T4 (thyroxine) and T3 (triiodothyronine). Para follicular cells of thyroid produce calcitonin.T3, T4 are iodinated amino acids of tyrosine, and are synthesized from thyroglobulin and iodine.

Thyroglobulin is a dimeric glycoprotein with two protein chains. There are 115 tyrosine residues in each molecule. A large part (70%) of iodine in thyroglobulin exists as inactive monoiodotyrosine, diiodotyrosine and rest is in the form of T3, T4.If iodine content is normal, the ratio of T3 to T4 is 7:1.In case of iodine deficiency, the ratio decreases.T3, T4 are stored in the thyroglobulin . The peptide bonds are broken before they are released into capillaries.

Synthesis of Thyroglobulin:

* The acinar cells of thyroid synthesize and store thyroglobulin as colloid in follicles.
* They also collect (Iodine trap) and transport iodine for the synthesis of hormone.
* They help in the secretion of T3, T4 into circulation.
* Thyroglobulins are packed into vesicles and pinched off from Golgi cisternae.
* These vesicles fuse with plasma membrane release their contents into the colloid of thyroid follicles.

Dietary iodine comes from vegetables, fruits, grown on sea shore. Sea fish is very rich in iodine. Total iodine in the body is 50 mgs and only.10-15mgs is in the thyroid. Daily requirement is 100-200µ g. In the kidneys 97% of filtered iodine is reabsorbed.

Thyroid concentrates iodine from circulation and transports to colloid. The required transporter pump is located on the plasma membrane which works along with sodium pump. The activity of the pump is stimulated by TSH. The iodine pool in acinar cells exists as exchangeable iodide in blood and unused iodine as iodotyrosine.

Oxidation of iodine is carried out by thyroperoxidase. The enzyme binds iodide to thyroglobulin at specific sites on the molecule.The iodine is added to the 3rd position of aromatic ring in tyrosine .It forms monoiodotyrosine (MIT) then it is iodinated at 5th position to form diiodotyrosine (DIT).

When 2 molecules of DIT undergo oxidative condensation in the presence of thyroperoxidases, T_4 is synthesized. The liberated iodine from thyroglobulin is reutilized. De-iodination converts T_4 to T_3 in other organs than thyroid.

TSH stimulates the synthesis of thyroglobulin and thyroxine.

T_3, T_4:

* 80 % of T_4 is converted to T_3.
* T_3 loosely bound to the serum proteins.
* T_3 is more active than T_4.
* T_3 has rapid onset of action.
* It is more rapidly degraded in the body.
* T_3 binds to thyroxine receptors in target tissues with higher affinity than T_4.
* Only free T_3, T_4 are the metabolically active hormones in plasma.

T3 appears to be the major thyroid hormone metabolically.

Mechanism of action of thyroid hormone:

Targets are liver, kidneys, adipose, cardiac, neurons, and lymphocytes.etc.

Nucleus has receptors for the T_3 and T_4, when the hormone binds to them.

* It Increases the gene transcription, and produce more proteins and enzymes.
* The hormone promotes protein synthesis.

Metabolic role:

* It favors protein anabolism and stimulates growth in children.
* The hormone increases glucose utilization and cholesterol , phospholipid synthesis.
* Thyroxine produces more heat by increasing O_2 consumption. Thus basal metabolic rate (BMR) is increased.
* Conversion of carotene to Vit.A requires thyroxine. Thus in hypothyroidism, there is accumulation carotene in blood which is responsible for the yellowish tint of the skin.

Hyperthyroidism: There is excess of T_3, T_4 due to enlarged thyroid, toxic goiter, thyrotoxicosis. In most cases, it could be due to Graves disease, which results from the over production of thyroid stimulating immunoglobulin (TSI). Antibodies are developed against thyroid due to autoimmunity.

Symptoms:

- Patient has protrusion of eye balls; in a condition called exophthalmoses. Eyeballs undergo edematous swelling.
- Patient suffers from rapid heart rate, increased BMR, loss of weight, and has marked nervous excitability, increased sensitivity to heat.
- Excessive sweating is common.
- Hyper glycemia, glucosuria and reduced glucose tolerance due to increased absorption of carbohydrate from intestine. Hyperthyroidism is treated with radioactive isotope like I^{131} or anti thyroid drugs improve the condition of the patient.

Anti thyroid drugs inhibit thyroid function by:

1. Interfering 'iodide trapping'
2. Inhibiting iodination and coupling during synthesis of hormone.
3. Inhibiting hormone release.
4. Inhibiting conversion of T_4 to T_3 in target tissues.

Hypothyroidism: Occurs due to insufficient free T3 or T4, mainly because of thyroid failure. It could be due to diseases of pituitary ,hypothalamus or autoimmunity.

- Patient has decreased BMR.
- Body temperature below normal.
- Heart rate is decreased, sluggish behaviour.
- In children it causes cretinism and in adults it causes myxedema.

Cretinism, is due to failure of growth and mental retardation. Cretinic child has congenital defects like short stature and stunted growth. It can be due to congenital absence of thyroid gland or from lack of iodine in the diet.

Goitre: It means enlarged thyroid gland. When there is iodine deficiency in the diet, patient develops endemic goitre. Iodine deficiency prevents the production of T_3, T_4 but does not stop production of thyroglobulin. So TSH is released in large quantities, which in turn stimulates secretion of thyroglobulin in to colloid of follicular cells. So the gland enlarges 20 times to that of normal.

Symptoms:

- Sleeping for long hours .
- Muscular sluggishness.
- Increased body weight, mental sluggishness, husky voice, scaly skin.
- The patient develops nonpitting, edema all over body, in a condition called Myxedema. There is increased level of hyaluronic acid and chondroitin sulfate bound to protein, which forms excessive tissue gel in the interstitial spaces.
- Symptoms of this condition are progressive mental retardation, slowing of body processes, weight gain, thinning of hair and swelling of tongue. Endemic goitre is treated with supplementation of diet with iodized salt. Simple goitre (deficiency of Iodine) may be treated with exogenous thyroid hormones.

Catecholamines

Synthesis: Epinephrine is synthesized, stored in adrenal medulla while nor- epinephrine is synthesized in sympathetic nervous system. They act as neurotransmitters. A small concentration is synthesized, stored in adrenal medulla. These two hormones are synthesized in Pheochromomcytes or neuroglial cells, from tyrosine. See the details of synthesis from amino acid chapter.

Both the hormones are stored as chromofin granules in adrenal medulla. In nerve tissue only nor- epinephrine is produced.

Since catecholamines can't cross blood -brain barrier, brain synthesizes its own nor epinephrine.

Metabolic role:

- In liver epinephrine stimulates glycogenolysis via c AMP, & increases Calcium levels.
- Norepinephrine has no effect on blood glucose, lactic acid levels. Glycogenolysis is increased in muscle by epinephrine.
- The same increases cardiac output, & glycogenesis in heart muscle. * Both the hormones promote lipolysis via c AMP.
- Epinephrine has inhibitory effect on insulin release.
- Both hormones promote metabolic rate through cutaneous vasoconstriction, which decreases heat loss and increases body temperature and muscular activity.


THANK YOU