Lecture no.-6

THYROID HORMONES

Synthesis

1. **Tyrosine+I= Monoiodotyrosine(MIT)**
2. **MIT+I=Di-iodotyrosine(DIT)**
3. **DIT+MIT=Tri-iodothyronine(T_3)**
4. **DIT+DIT=Tetraiodothyronine(T_4) or Thyroxine**

Thyroxine is predominant in all animals, i.e.,

SN.	**T_3 (10%)**	**T_4 (90%)**
	Half life- 1 Day	Half life- 6-7 Day
	More Active&potent (4 times)	Less active &less potency
	Less binding capacity with protein	More binding capacity with protein And strongly bind with plasma protein and duration of action 4x than T_3
	Less concentration(.064-1ng/ml)	More concentration(15-44ng/ml)

- In the blood, the thyroid hormone is transported bound with a serum globulin, the thyroid-binding globulin (TBG - present in all animals except cat).
- In many species, thyroid hormones are also transported with an albumin, the *thyroid-binding pre-albumin* (TBPA also termed as **transthyrectin – specifically transports T4)** and albumin itself is a thyroid hormone carrier;

MORPHOLOGICAL (GROWTH AND DEVELOPMENT) EFFECTS

- Thyroid hormones are required for **normal growth and skeletal maturation**.
- They **potentiate the effects of GH and act in synergy with GH in promoting normal growth of animals**.
- TH is required for maturational changes in vertebrates and helps the growth of the young birds and mammals. **Even though GH stimulates growth, for differentiation thyroid hormones are essential**.
- TH helps in **metamorphosis in amphibians.**
- Thyroxine administration causes **differentiation of tadpoles into frogs.**
- Thyroxine controls the growth and eruption of the teeth and also horns in sheep and antlers in deer. **Hypothyroidism severally retards the eruption of permanent teeth**.
- **TH is also necessary for the normal development of nervous tissue in fetus and neonates**.
- **Thyroid deficiency in young leads to retardation of mental activity.**
- **TH acts synergistically with sex steroids to function in growth and maintenance of comb in cock and moulting of feathers in birds**.

- In mammals, **renewal of epidermis and hair follicles are affected by thyroxine**.
- Thyroidectomized cattle and sheep have thinner hairs, which are coarse and brittle. In growing lamb, thyroxine deficiency may severally impair the quality of the adult fleece.
- In human beings and sometimes in dogs, hypothyroidism causes subcutaneous *oedema* due to accumulation of mucopolysaccharide rich material under the skin. This condition is called as myxedema.
- Myxedema and *alopecia(partial or complete absence of hair from areas of the body)* have also been observed in calves and pigs born to iodine-deficient mothers.
- TH helps the normal process of spermatogenesis, folliculogenis, and maturation of follicle, ovulation and maintenance of a healthy pregnant state.
- ***Reproductive failure*** **is often a major sign of thyroid deficiency**. Iodine deficiency causes birth of excessive numbers of weak or dead young. Abortion, stillbirth, and the live birth of weak young are the major problems of hypothyroidism. Less severe deficiency will result in delayed puberty, irregular estrous, anestrus, and reduced fertility in the females and decreased testicular growth, impaired spermatogenesis and lowered libido in males. In rams, a seasonal reduction in semen quality has been associated with hypothyroidism.
- The accessory reproductive glands, which are most sensitive to the effect of the thyroid hormone, are the mammary gland.
- **Thyroxine is a powerful *galactopoietic* agent**;
- Thyromimetic agents have been tried as a means of increasing milk production. **Iodinated casein fed to cattle increased milk production by 10-30 %.**

FUNCTIONAL (METABOLIC) EFFECTS

1. Thyroid hormone **increases the metabolic rate and stimulates growth in young ones**.
2. **It increases the rate of O_2 consumption (up to 200%) and heat production which is known is calorigenic effect.**
3. Thyroid activity increases following **low environmental temperature, thus involved in thermo-regulation to *increase internal heat production* by non-shivering thermogenesis**
4. **It causes increased metabolic activities in almost all tissues of body except the brain, retina, spleen, testes and lungs**.
5. It increases the size and number of mitochondria to increase the ATP production.
6. It increases the activities of the respiratory enzymes and enzymes involved with glucose oxidation and gluconeogenesis.
7. It stimulates Na^+-K^+ ATPase activities, favours cations transport and thus stimulates mitochondrial O_2 utilization.
8. BMR is greatly increased by Thyroid hormone **.**
9. Thyroid hormone **increases cardiac output** ensuring sufficient O_2 delivery to the tissues.
10. Thyroid hormone **increases glucose absorption** from the intestine and facilitates insulin-mediated glucose absorption by the cells and produces glycogenolysis.
11. **Thyroid hormone increases protein synthesis by stimulating mRNA synthesis and the rate of formation of proteins (enzymes) by ribosomes.**

12. It **enhances the actions of catecholamines** which include non-shivering thermogenisis, lipolytic, glycogenolytic, gluconeogenic and insulin secretion .
13. Thyroid hormone potentiates the **stimulatory effects of other hormones on metabolism** by increasing the uptake of glucose by cells, enhanced glycolysis, gluconeogenesis, and absorption from gastro-intestinal tract lipolysis,etc.
14. Thyroid hormone lowers blood cholesterol level due to increased removal by liver, mobilizes fat for energy, depletes fat stores of the body.
15. One of the major metabolic results of thyroid deficiency is a marked increase in the serum cholesterol, phospholipids, triglycerides and decreased free fatty acid levels.
16. The thyroid hormones influences nervous functions at all levels.
17. Thyroxine enhances the speed and amplitude of reflexes, wakefulness, alertness to various stimuli, awareness of hunger, memory and learning capacity.
18. Thyroid deficiency is a major factor for obesity and increased body weight.

HYPERTHYROIDISM

- *Hyperthyroidism:* The entire thyroid gland is hyperplastic, increase in size to two to three times normal; cell number is also increased with increase in secretion rate.
- These changes are brought about by antibodies (thyroid stimulating antibodies -TSI) that bind with thyroid cell membrane receptors similar to TSH and induce continual activation of the cells. The antibodies develop as autoimmunity against TSH receptors. This condition is called as toxic goitre

or thyrotoxicosis or Grave's Disease in human beings. Plasma TSH level is usually low.

- Hyperthyroidism occurs in toxic goitre and thyroid tumours of older cats.
- *Symptoms:* Intolerance to heat, increased sweating, weight-loss, diarrhoea, muscle weakness, psychic disorders etc. In hyperthyroidism protrusion of eyeball occurs - called as exophthalmous.
- *Treatment*for hyperthyroidism is surgical removal of the thyroid gland; injection of radioactive iodine (I2 taken by the gland and radioactivity destroys the gland cells).

HYPOTHYROIDISM

- Goitre means enlarged thyroid gland.
- Insufficient I_2 intake in animals and man leads to goitre known as **endemic goitre**.
- Lack of I_2 reduces thyroid hormone synthesis and the reduced blood TH enhances TSH from adenohypophysis. The TSH stimulates the thyroid gland to secrete excess thyroglobulins into the follicles and the gland grows very large. But the thyroid hormone secretion cannot be increased due to lack of I_2 leading to further increase in TSH secretion. Hence this condition is called as endemic colloid goitre.
- Mild thyroiditis causes slight hypothyroidism which leads to increased TSH secretion and the gland enlarges producingnon-toxic or colloid goitre.
- Hypothyroidism is common in dogs.
- Ingestion of goitrogenic substances also causes goitre.

Symptoms

- Fatigue, somnolence(**sleepiness)** is a state of near-sleep, a strong desire for sleep, or sleeping for unusually long periods, muscular sluggishness,

reduced heart rate, decreased blood volume, increased weight, constipation, mental sluggishness, hair falling and edematous appearance of whole body, bagginess of eyes, and swelling of face. Increased quantities of mucoplysaccharides accumulate in the interstitial spaces leading to myxedema.

- When hypothyroidism is severe during foetal life, infancy and in young age especially in humans, there is failure of body growth and CNS development is impaired with brain hypoplasia and this condition is called as cretinism – physical and mental growth are retarded; skeletal growth is inhibited, soft tissues enlarge greatly and the cretin appears obese and stocky.

Treatment

- Oral ingestion of thyroid hormone.
- Hypothyroidism results in retarded growth while in hyperthyroidism, excessive skeletal growth in young animals.

ANTITHYROID COMPOUNDS

- Drugs or agents that depress the thyroid secretion are called as antithyroid compounds.
- The major cause of goitre in man and farm animals is a simple dietary iodine deficiency.
- Certain foodstuffs contain substances that inhibit thyroid activity.
- This goitrogenic activity is seen in feeding of cabbage, and other cruciferous plants, e.g., turnip, soybeans, linseed, peas, rapeseed, mustard seed and peanuts.
- A potent goitrogenic compound, goitrin, is responsible for most of the antithyroid activity of the rapeseed, mustard seed. However, the

goitrogenecity of many plants is also due to the presence of other goitrogens such as thiocyanate.

- Since thiocyanate and other chemical radicals interfere with the trapping of iodine by the thyroid gland, the goitrogenicity of these radicals can be overcome by feeding excess iodide.
- It is more difficult to overcome the effect of goitrin and related compounds, since they interfere with the organic binding of iodine and not with the iodine trap.
- Other anti thyroid compounds includes **sulfonamides, D-amino salicylate and chlorpromazine**.
- The compounds exerting the most potent antithyroid activity are the thiocarbamides, thiourea and thiouracil compounds which inhibit either the conversion of iodide to iodine or the organic binding of molecular iodine with tyrosine or the conversion of T_4 to T_3.
- These antithyroid substances are useful in the treatment of hyperthyroidism.

ROLE OF CALCIUM AND PHOSPHORUS

- Calcium is important for
    - Muscle contraction
    - Nerve cell activity
    - Release of hormones by exocytosis
    - Activation of number of enzymes
    - Coagulation of blood
    - Maintaining stability of cell membrane
    - Maintaining structural integrity of bone and teeth
- Phosphate is important for

- Structure of bone and teeth
- As part of cell membrane organic PO4
- As part of number of intracellular components

- About 99% of the body's Ca^{2}+ is in the bone and a very small amount is in the plasma (1%).
- In most animals and in non-laying birds the blood Ca ranges between 7.9 and 11.7 mg/dl except in horses in which it is between 10.4 and 13.4 mg/dl and in layers 17-39mg/dL.
- In bones there are two types of cells –*osteoblasts* and *osteoclasts* that are responsible for bone formation and bone reabsorption respectively.
- Osteoblasts are bone forming cells.The osteoblasts after the formation of organic matrix are fixed into the matrix and termed as *osteocytes.*

CHEMISTRY

- Parathyroid hormone (PTH) is a single chain polypeptide containing 84 amino acids.
- PTH is synthesized as part of a large molecule containing 115 amino acids called *pre pro-parathyroid hormone* (pre-pro PTH) by the ribosome.
- This large molecule is converted to *pro-PTH* composed of 90 amino acids in the rough endoplasmic reticulum. It moves to the Golgi apparatus and is enzymatically cleaved to produce the biologically active PTH.
- Active PTH may be secreted directly or packaged into secretory granules.

REGULATION OF PTH SECRETION

- Parathyroid hormone has a unique feedback control by the concentration of calcium and to a lesser extent magnesium ion in serum.
- Low blood level of *ionized* Ca^{2+} stimulates rapid release of parathyroid hormone

- Calcium has a negative feedback effect on PTH release.
- Magnesium ion has an effect on parathyroid secretory rate similar to that of calcium, but its effects is not equipotent to that of calcium.
- The concentration of blood phosphates has no direct regulatory influence on the synthesis and secretion of PTH.
- PTH is essential for life.

BIOLOGICAL EFFECTS

- Parathyroid hormone is the principal hormone involved in the *minute-to-minute* and fine regulation of blood calcium level in mammals.
- It exerts its biological action by directly influencing the function the bone and kidney and indirectly in the intestine to maintain plasma Ca level

On bone

- Osteoclasts not have PTH receptors only osteoblasts having PTH receptor
- osteoblast-binding with PTH indirectly stimulated Osteoclasts. And they cause
- *Osteoclastic osteolysis:* PTH activates osteoclasts to cause the breakdown of bone and releases Ca into the blood

On kidney

- It increases tubular reabsorption of calcium,
- It increases urinary excretion of phosphates, (phosphaturia), K^+,bicarbonate, Na^+ and amino acids.
- PTH activates 1 α - hydroxylase to convert 25 hydroxy cholecaliferol to 1, 25 dihydroxycholecaliferol (vitamin D_3) in the kidney.

On intestine

- Promotes absorption of Ca and PO_4 from GI tract by activating 1, 25 DHCC.

On Blood

- Elevates the blood Ca concentration and decreases the blood PO_4 concentration.

CHEMISTRY AND REGULATION OF SECRETION OF CALCITONIN

- Calcitonin (thyrocalcitonin) is secreted in the mammalian thyroid gland by *parafollicular* or 'C' cells of thyroid gland which are found in the interstitial tissue between the follicles.
- In reptiles, amphibians and birds, CT is secreted from ***ultimobranchial glands***.

Chemistry of Calcitonin

- Calcitonin is a polypeptide hormone composed of 32 amino acid residues arranged in a straight chain with a1-7-disulphide linkage.
- The structure of calcitonin differs significantly between species.

Regulation of Calcitonin Secretion

- Hypercalcemia and to a lesser extent increased levels of blood magnesium will stimulate CT secretion.
- The gastro-intestinal hormones Glucagon, gastrin, secretin and CCK produced by the presence of food in the GI tract are the stimulants for CT release.
- Glucagon with gastrin provides the most potent stimulation in the secretion of CT.
- CT protects the skeleton during Ca stress like during growth, pregnancy and lactation.

BIOLOGICAL EFFECTS OF CALCITONIN

- **Calcitonin is calcium lowering hormone**.

1. With respect to plasma Ca level, CT antagonises the actions of PTH by inhibiting osteoclastic bone resorption.

2. **Increased blood calcium level is the principle stimulus of CT release**.
3. **Osteoclasts have receptors for calcitonin**. CT decreases bone resorption through an inhibitory effect on osteoclasts.
4. CT increases Ca^{2+} excretion through kidneys.

PHYSIOLOGICAL SIGNIFICANCE OF CALCITONIN AND PTH

- Calcitonin and parathyroid hormone provide a *reciprocal inhibitory control mechanism* to maintain the concentration of calcium in extracellular fluids within narrow limits.
- Parathyroid hormone is the major factor concerned with the minute-to-minute regulation of blood calcium under normal conditions.
- ***CT is a short-termregulator* of blood calcium and it operates more rapidly compared with PTH**.
- CT function more as an emergency hormone to prevent the development of hypercalcemia.

CALCITRIOL

- The third major hormone involved in the regulation of calcium metabolism is *calcitriol* or *cholecalciferol* (vitamin -D_3)
- Cholecalciferol is ingested in the diet and also synthesized from 7-dehydrocholesterol by ultraviolet irradiation.

BIOLOGICAL EFFECTS

- In the kidney 1, 25 DHCC is transported in a protein-bound form which is known as *transcalciferin* (a -globulin) to specific target cells in the intestine and bone.
- In the intestine, it stimulates increased synthesis of vitamin-D dependent proteins such as *Calcium Binding Protein* (CaBP) and *calmodulin* by intestinal cells which contributes to increased intestinal absorption of Ca.

- It also promotes intestinal absorption of phosphorus.
- Calcitriol is also necessary for osteoclastic resorption and Ca mobilisation from bone.
- It increases the reabsorption of Ca from kidney.
- An increase in 1, 25 DHCC inhibits the secretion of PTH.
- Calcitriol has permissive effect on PTH activity on osteoclasts

PARTURIENT HYPOCALCEMIA IN DAIRY COWS

- *Parturient hypocalcemia* is a metabolic disease of high producing dairy cows characterized by the development of severe hypocalcemia, hypophosphatemia near the time of parturition.
- Total and ionized calcium levels in plasma decrease progressively beginning several days before parturition.
- Calcium homeostasis in pregnant cows fed a high Ca diet appears to be maintained principally by intestinal Ca absorption.
- Feeding balanced or relatively low Ca diets during prepartum (last two weeks of gestation) prevents this disorder by mobilizing the required level of calcium from the bony matrix.

PUERPERAL TETANY OR ECLAMPSIA

- This condition is seen in small hyper excitable breeds of dogs.
- The bitch may develop severe hypocalcemia and often hypophosphatemia near the time of peak lactation (1-3 weeks) postpartum which is the result of failure of calcium homeostasis.
- This failure is due to low Ca^{2+}inflow to the body and high outflow of Ca^{2+} in the milk.

- There will be restlessness, panting, nervousness, trembling, muscular tetany and convulsive seizures in 8- 12hours.
- Administration of intravenous Ca^{2+}combined with temporary removal of pups to reduce lactational drain of Ca^{2+}will correct this problem .
- Vitamin D deficiency leads to poor intestinal absorption of Ca with poor mineralization of bone leading to rickets in young animals and children and *osteomalacia* is adults .