

Title: Thyroid Gland & Hormonal Control of Calcium Metabolism

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I. The Thyroid Gland

- 1. The thyroid gland (follicular cells) produces and secretes *thyroxine (T₄)*, *triiodothyronine (T₃)* and reverse *triiodothyronine (rT₃)*.**
- 2. Parafollicular (C) cells of the thyroid gland produce and secrete *calcitonin*.** Calcitonin is involved in the regulation of calcium metabolism.
- 3. *T₃* is more active than *T₄*, while *rT₃* is inactive. All these hormones are composed of iodine – containing tyrosine residues.**
- 4. The average diet contains 500 µg of iodine, while 150 µg per day is the minimal iodine intake that is necessary to maintain thyroid function.**
- 5. About 90% of the thyroid hormone secreted by the gland is *T₄* while 10% is *T₃*. In the target cells, *T₄* is converted to either *T₃*, or *rT₃*.**
- 6. Synthesis and secretion of thyroid hormones:**
 - a. Synthesis of thyroglobulin in the follicular cells.
 - b. An active transport of iodides from the extracellular fluid into the follicular cells - “*iodide trapping*” (“*iodide pump*”).
 - c. *Conversion of iodide ions to an oxidized form of iodine.*
 - d. *Binding of iodine with thyroglobulin* - formation of *monoiodotyrosine (MIT)* and *diiodotyrosine (DIT)*.
 - e. *Coupling reactions* resulting in the formation of *T₄*, *T₃* or *rT₃*.
 - f. Storage of the thyroid hormones in the follicular colloid.

Iodide oxidation, binding of iodine with thyroglobulin and probably coupling reactions are promoted by the *thyroid peroxidase*.

7. Secretion of thyroid hormones requires formation of pinocytic vesicles, and then the digestive vesicles. Lysosomal proteases digest the thyroglobulin and liberate the thyroid hormones. About 75% of iodinated (but uncoupled) tyrosine residues is deiodinated by thyroid deiodinase and their iodine is again used to produce thyroid hormones.

8. Iodide deficiency inhibits the function of the gland, as does high plasma level of iodides.

9. The synthesis and secretion of thyroid hormones are stimulated by pituitary thyroid stimulating hormone (TSH).

10. Most (over 99%) of the circulating hormones is bound to the plasma proteins: TBG (thyroxine-binding globulin), transthyretin - TBPA (thyroxine-binding prealbumin) and albumin.

11. T_4 is the principal hormone secreted by the thyroid gland. T_3 is the major hormone that acts on the target cells.

- a. The binding affinity of TBG and other plasma proteins is over 6 times greater for T_4 than for T_3 thus *the biologic half-life of T_4 is 6-7 days, while that of T_3 is 1 day.*
- b. Triiodothyronine provides 90% of thyroid hormone molecules that bind with the hormone receptor.

12. Effects of Thyroid Hormone

The thyroid hormone:

- a. **causes nuclear transcription of large numbers of genes and consequently, an increase in the formation of many proteins**, including enzymatic structural, and other proteins. *The major effects of T_3 on target cells are to increase the rate of metabolism, oxygen consumption, and energy (ATP and heat) production in the cell, accounting for the calorogenic effect of the hormone.* This effect is stimulated by cold weather and pregnancy. However, BMR and oxygen consumption in the brain, pituitary, gonads, spleen, and lymph nodes are not affected.
- b. *increases body requirement of vitamins.*
- c. *stimulates almost all aspects of carbohydrate metabolism and carbohydrate absorption from the gastrointestinal tract.*
- d. *increases plasma free fatty acids` level and decreases plasma cholesterol level.*
- e. *increases both protein synthesis and protein break down.*
- f. *inhibits the synthesis and increases degradation of mucopolisaccharides and fibronectin (connective tissue).*
- g. *increases the rate of blood flow in the tissues; cardiac output (heart rate and stroke volume) and the systolic pressure.*
- h. *increases the rate and depth of breathing.*
- i. is permissive to action of the growth hormone, *is essential for normal growth and skeletal maturation.* Thyroid hormone stimulates ossification of cartilage, linear growth of bone, maturation of the epiphyseal bone centers and closure of epiphyses.
- j. *is essential for normal growth and development of brain. It`s deficiency at birth (congenital hypothyroidism) and/or during infancy or childhood causes mental retardation (cretinism), retarded growth rate, lower body temperature, and thickened facial features.*
- k. *increases rapidity of cerebation.*
- l. *increases both the secretion and motility of the gastrointestinal track.*
- m. *affect the function of other endocrine glands.*
- n. *affects the function of the reproductive system.*

13. Thyroid Disorders – Hyperthyroidism

- a. *The major cause of hyperthyroidism is Graves` disease* (toxic goitre).
- b. Other causes of hyperthyroidism include solitary toxic adenoma, toxic multinodular goitre, or TSH – secreting pituitary tumor.

14. Thyroid Disorders - Hypothyroidism

- a. Hypothyroidism may result from autoimmune thyroiditis (Hashimoto disease), head or neck irradiation, or deficiency of TSH.
- b. *Congenital hypothyroidism.*

15. *Goitre is a pathological enlargement of the thyroid gland.* Endemic goitre is caused by insufficient dietary intake of iodine. Toxic goitre is found in Graves` disease.

II. Hormonal Control of Calcium Metabolism

A. Calcium Homeostasis

1. **The majority of the total body calcium is stored in the bones, about 1% - is present in the cells, and 0,1% - in the extracellular fluid.**
2. **About 41% (1 mmol/L) of plasma calcium is combined with the plasma proteins, 9% (0,2 mmol/L) is bound to the anions (citrate, phosphate), and 50% (1,2 mmol/L) is in the ionized form. Free, ionized Ca^{2+} is biologically active and its concentration is regulated very precisely.**

B. Parathyroid Hormone (PTH)

1. **PTH is produced and secreted by the parathyroid glands.** It contains 84 amino acids.
2. ***The parathyroids secrete PTH in response to a decrease in calcium ion concentration in the extracellular fluid (hypocalcemia).*** Parathyroid glands enlargement occurs under conditions of their prolonged stimulation (rickets, pregnancy, and lactation). Conditions associated with increased calcium ion concentration (enhanced vitamin D and/or calcium intake, bone absorption, which does not result from PTH action) cause decreased activity and reduced size of the glands. Mild decrease in serum Mg^{2+} level stimulates PTH secretion while severe decrease inhibits PTH secretion and produces symptoms of hypoparathyroidism.
3. ***PTH causes an increase in calcium ion concentration in the extracellular fluid and a decrease in phosphate level. These effects result from PTH action on three target organs: bone, kidney, and intestine.*** The last effect is indirect; PTH increases formation of the active form of vitamin D, which promotes calcium and phosphate absorption by the intestine.

4. Effects of PTH on Bone and Kidney:

- a. *The first (rapid) phase results from activation of already existing bone cells (the osteocytic membrane system) and absorption of calcium phosphate salts from amorphous compounds without resorption of the organic matrix (osteolysis).*
- b. *The second phase results from activation of the osteoclastic system. The proteolytic enzymes and acids released from the osteoclasts cause reabsorption of the bone itself, which is reflected by increased hydroxyproline excretion in the urine.*
- c. *Alone, these effects would not increase the ionized calcium in the plasma, because phosphate complexes with calcium ions.*
- d. *In the kidneys, PTH increases the reabsorption of calcium, mainly in the distal tubules, the collecting tubules, the early collecting ducts, and possibly, the ascending loop of Henle. PTH inhibits the reabsorption of phosphate in the early proximal tubules thus increasing phosphate excretion in the urine (a phosphaturic effect).*

C. Vitamin D

- 1. Vitamin D is present in the food, of either animal, or plant origin** (called cholecalciferol – D₃, or ergocalciferol – D₂, respectively). **Cholecalciferol is produced in the human body** from a precursor present in the skin (7 – dehydrocholesterol). Ultraviolet rays cause its conversion to vitamin D₃.

- 2. Vitamin D itself is not active and must be converted, via two subsequent hydroxylation, into the active form.**
 - a. First hydroxylation occurs in the liver, where cholecalciferol is converted to 25-hydroxycholecalciferol that, in a feedback effect, inhibits this reaction.
 - b. Second hydroxylation occurs in the kidneys (the proximal tubules). Dependently on body need, 25-hydroxycholecalciferol is converted to either *1,25 - dihydroxycholecalciferol - 1,25(OH)₂D₃*, which is the most active form of vitamin D, or *24,25-dihydroxycholecalciferol - 24,25(OH)₂D₃*, which has almost no vitamin D effect. *PTH activates 1 α -hydroxylase.*

3. Vitamin D action:

- a. *In the intestines, $1,25(OH)_2D_3$ promotes absorption of calcium* (by increasing formation of a calcium binding protein in the intestinal epithelial cells) and phosphate.
- b. In the kidneys, vitamin D has a very weak effect on the reabsorption of both calcium and phosphate.
- c. In the bone, vitamin D is necessary for either bone deposition, or bone absorption

D. Calcitonin

- 1. Calcitonin is a 32-amino acid peptide produced in the parafollicular cells (C cells) of the thyroid.**
- 2. Calcitonin has weak effects opposite to those exerted by PTH.**
- 3. Calcitonin decreases blood calcium ion concentration;** it decreases the activity and formation of the osteoclasts and, possibly, the effect of the osteocytic membrane system. An increase in plasma calcium ion concentration stimulates the secretion of hormone.