Physiology for Medical Students

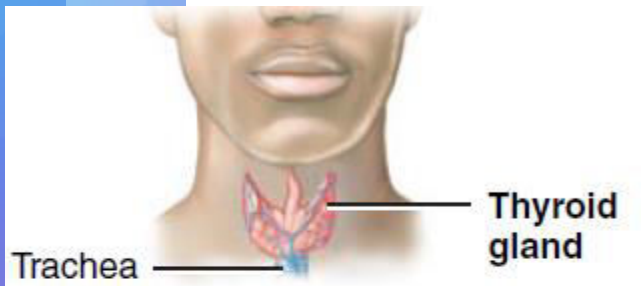
Endocrine 4

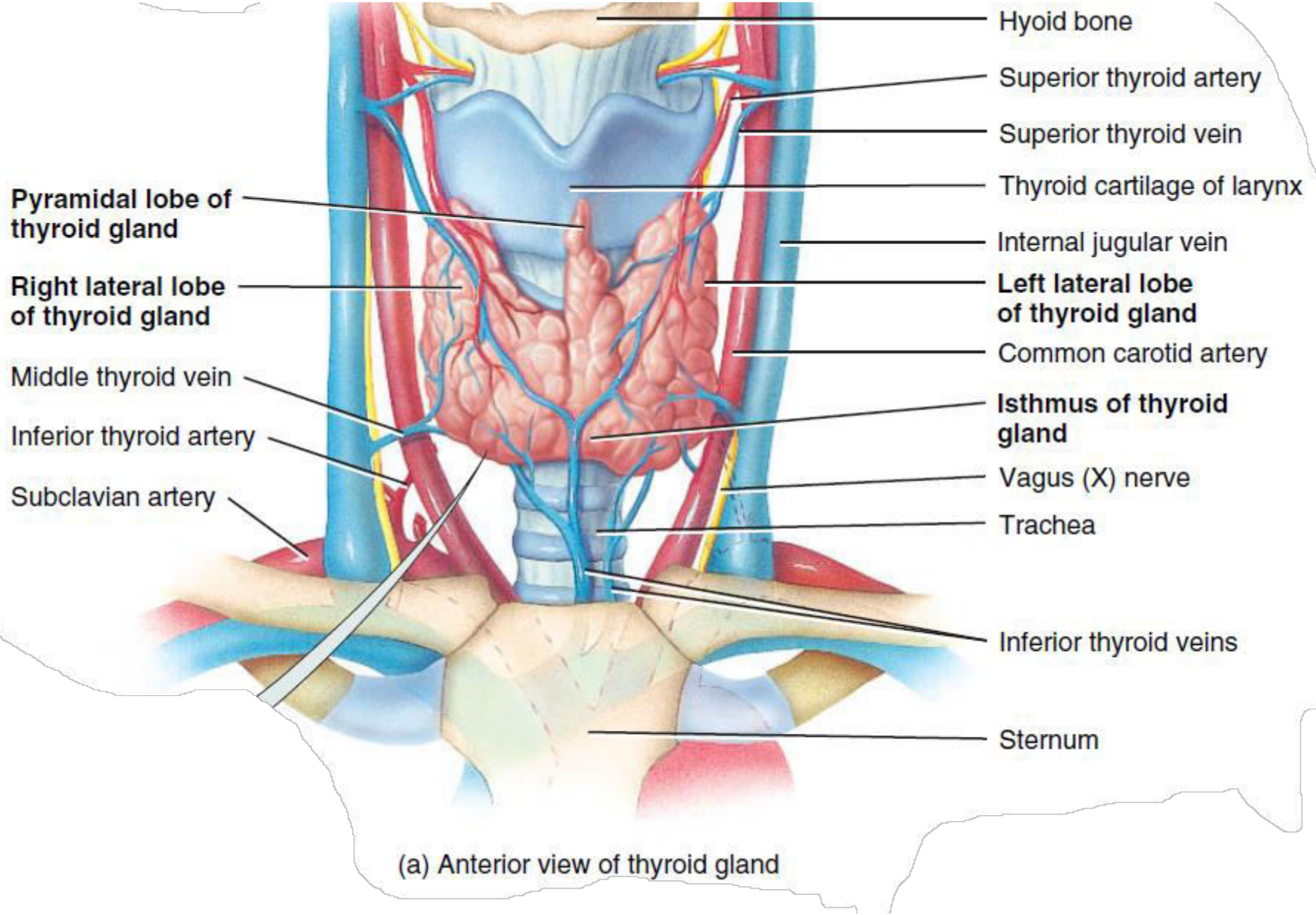
Fatima Daoud. MD. PhD.

Thyroid Metabolic Hormones

CHAPTER 77 , 14th edition

Thyroid gland





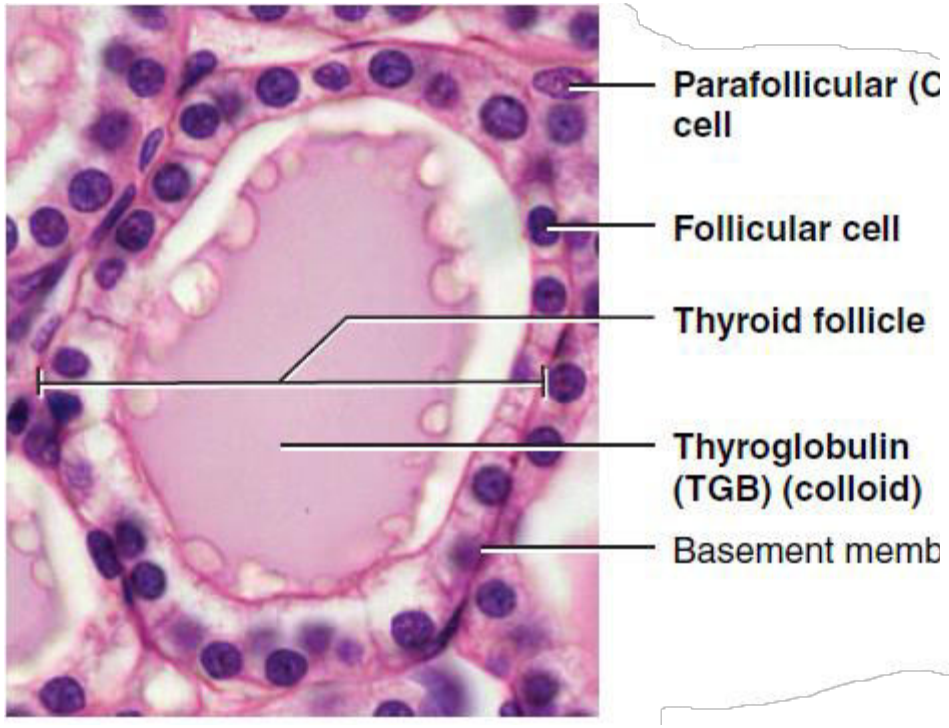
(a) Anterior view of thyroid gland

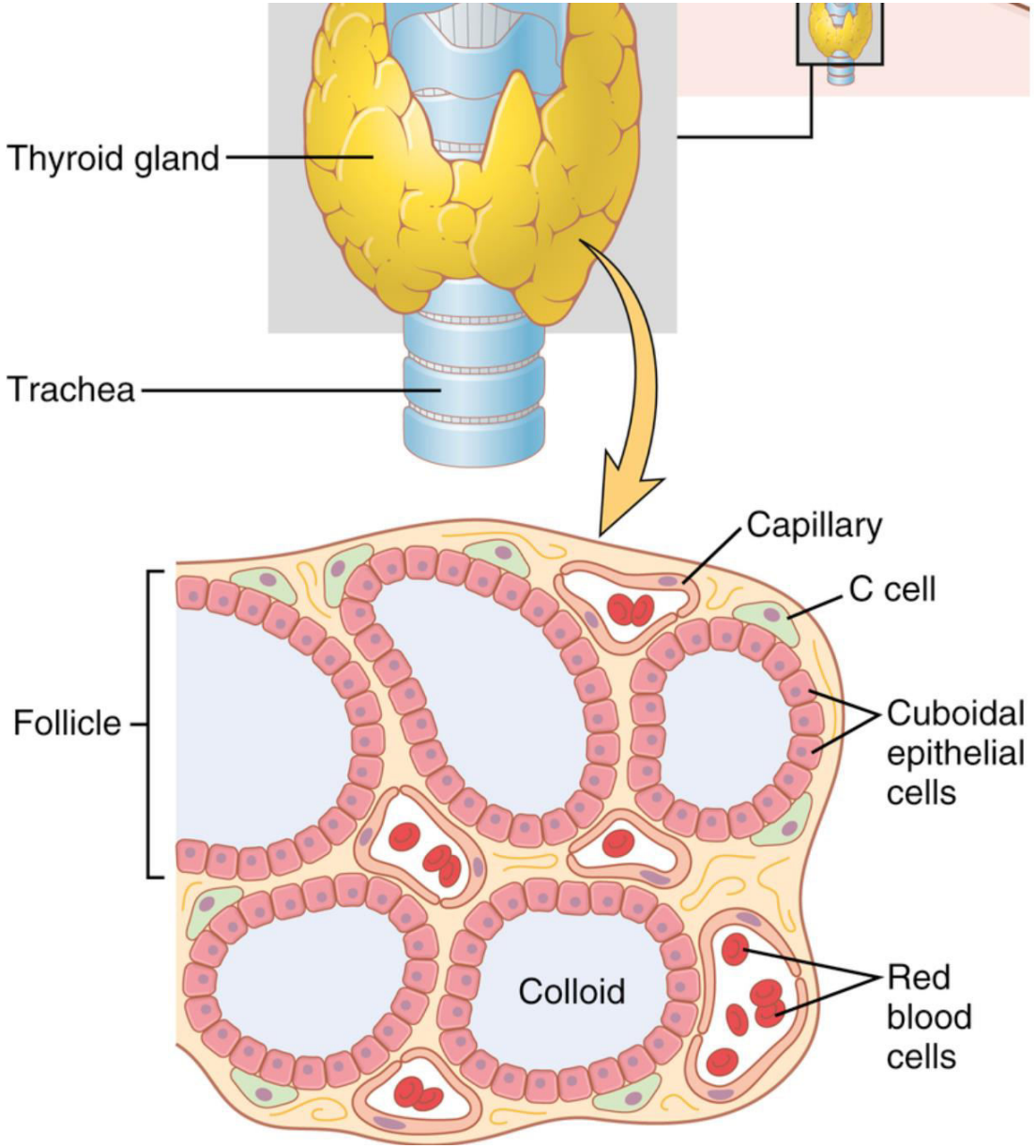
**The thyroid gland, located immediately below the larynx on each side of and anterior to the trachea.

** is one of the largest of the endocrine glands, normally weighing 15 to 20 grams in adults. The

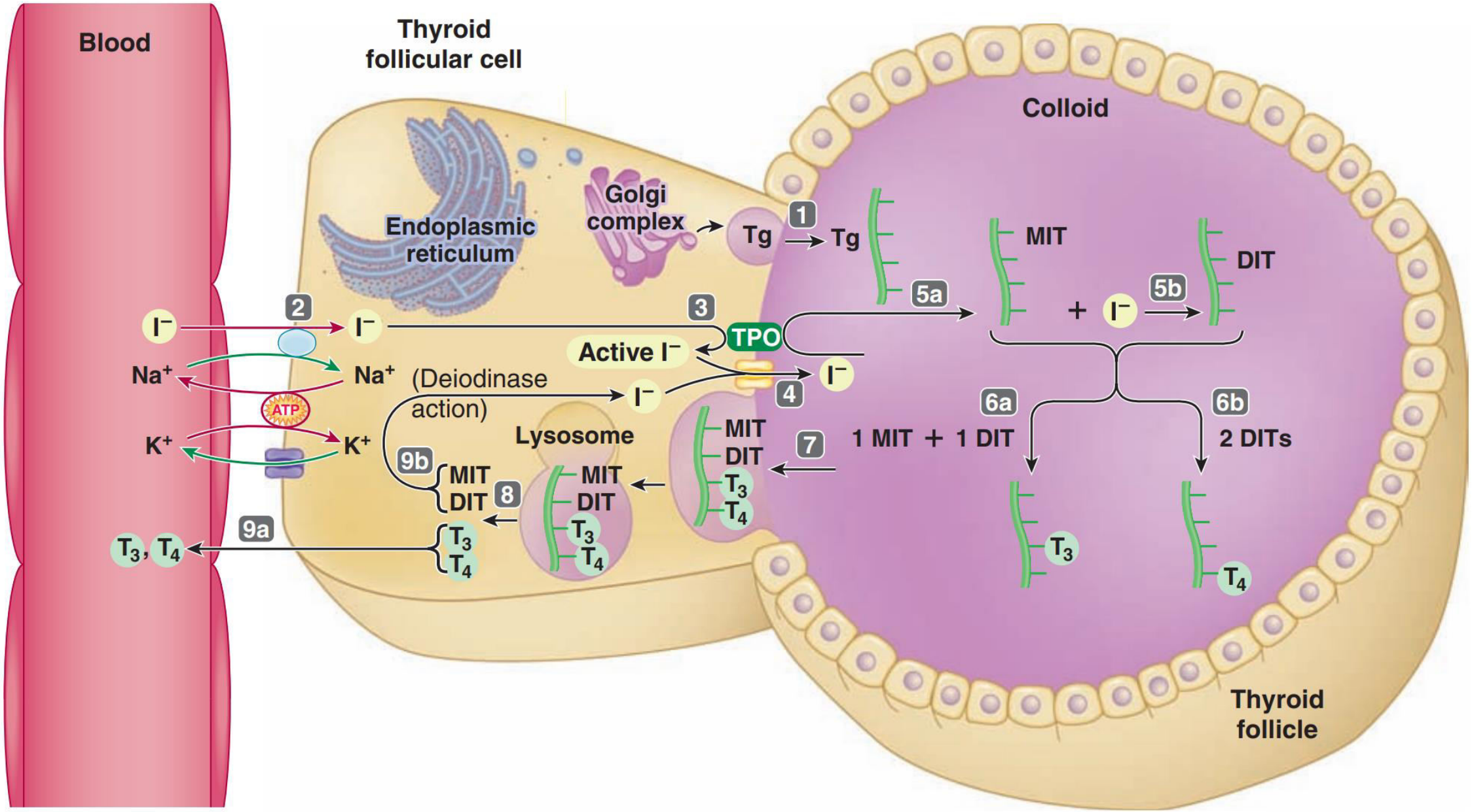
Thyroid gland

- Thyroid follicles produce thyroid hormones
- Parafollicular cells or C cells produce calcitonin





Synthesis and Secretion of the Thyroid Metabolic Hormones


Blood
Thyroid follicular cell
Colloid
Endoplasmic reticulum
Golgi complex
Tg
Tg
1
2
3
I⁻
I⁻
I⁻
Na⁺
Na⁺
ATP
K⁺
K⁺
TPO
Active I⁻
(Deiodinase action)
I⁻
4
5a
MIT
DIT
5b
+ I⁻
6a
6b
1 MIT + 1 DIT
2 DITs
7
MIT
DIT
T3
T4
Lysosome
9b
MIT
DIT
8
MIT
DIT
T3
T4
9a
T3, T4
T3
T4
Thyroid follicle

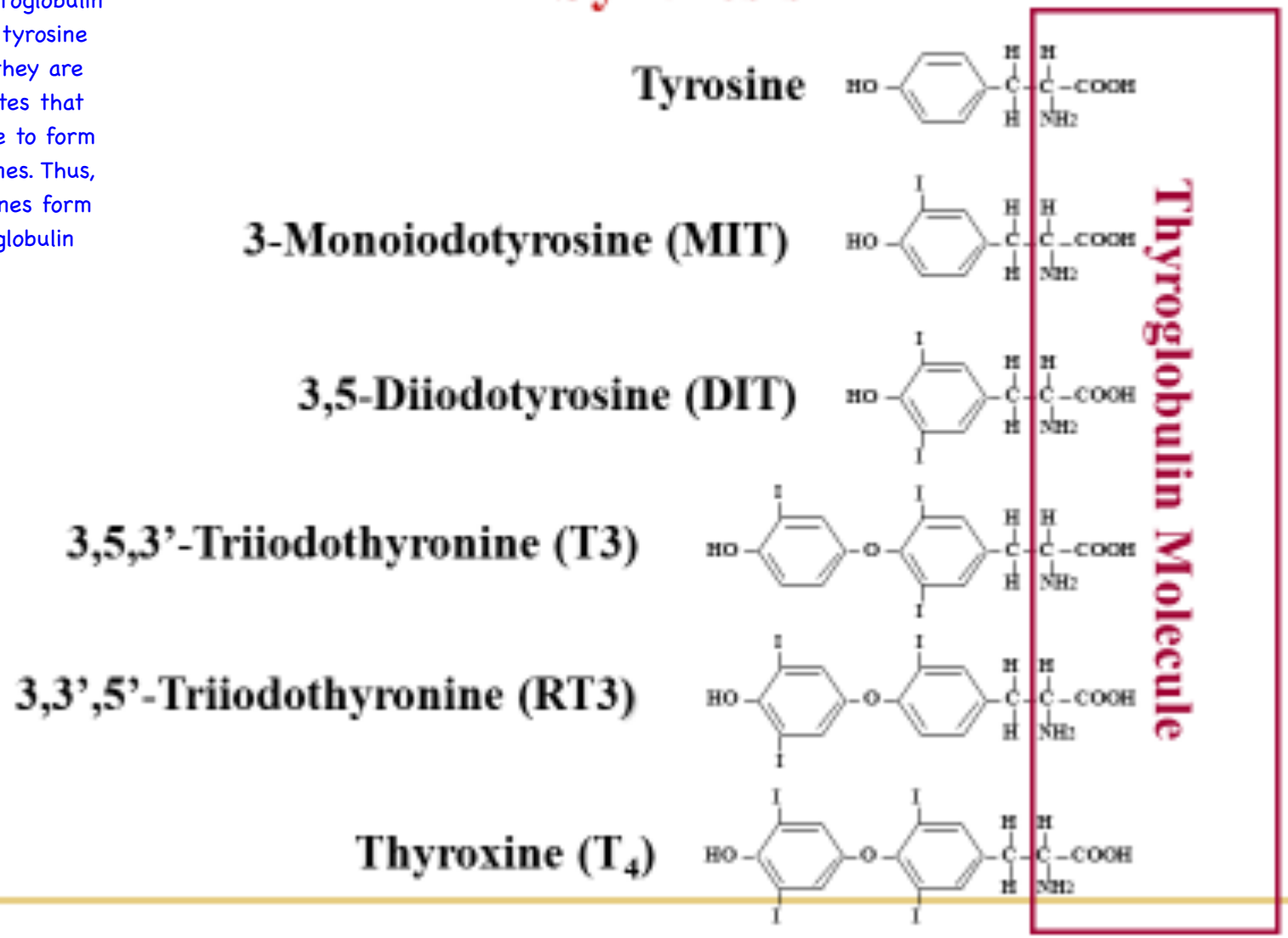
**about 93% of the metabolically active hormones secreted by the thyroid gland is thyroxine and 7% is triiodothyronine. However, almost all the thyroxine is eventually converted to triiodothyronine in the tissues, so both are functionally important.

** The functions of these two hormones are qualitatively the same, but they differ in rapidity and intensity of action.

**Triiodothyronine is about four times as potent as thyroxine, but it is present in the blood in much smaller quantities and persists for a much shorter time compared with thyroxine.

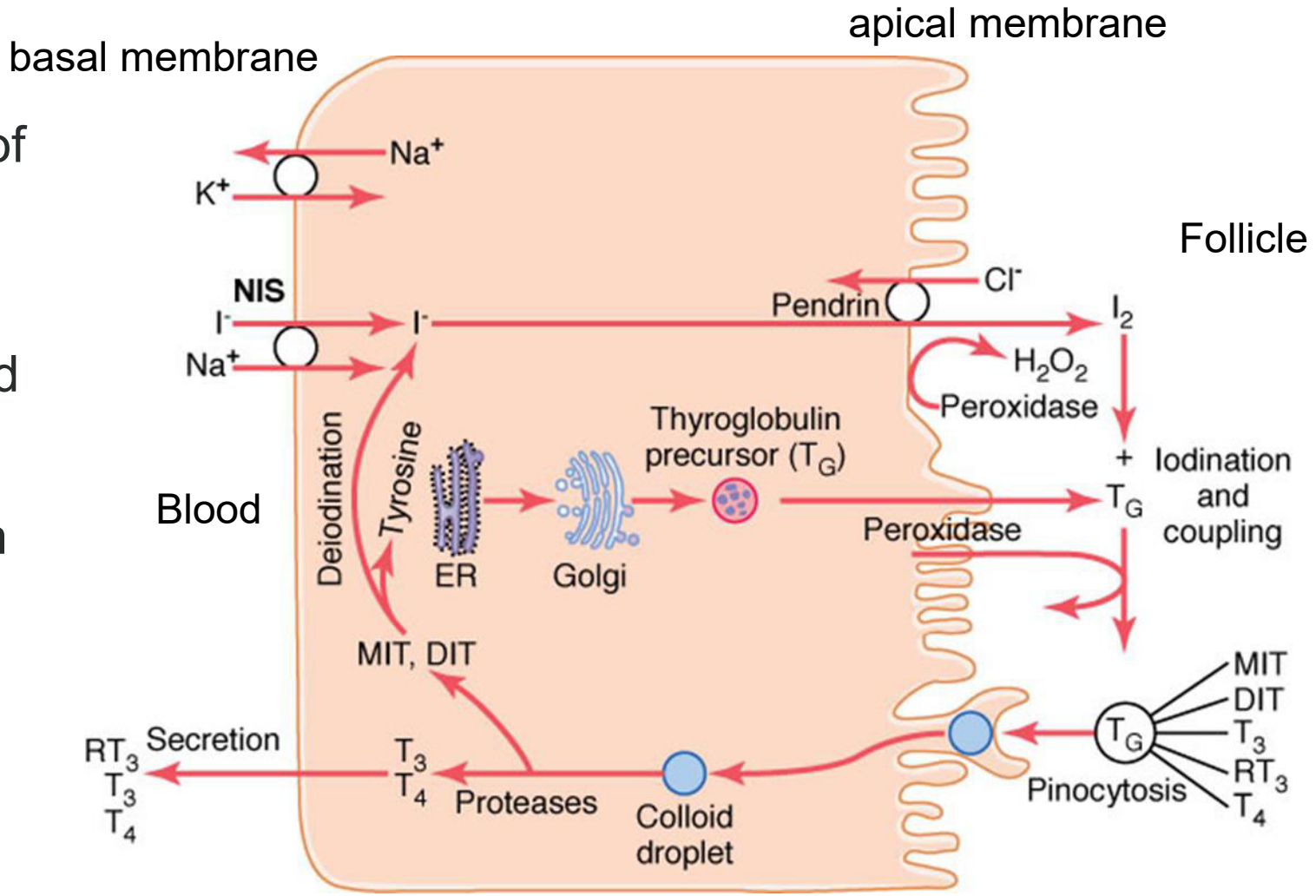
Binding of THs & Precursors to TG During Hormone Synthesis

ach molecule of thyroglobulin contains about 70 tyrosine amino acids, and they are the major substrates that combine with iodine to form the thyroid hormones. Thus, the thyroid hormones form within the thyroglobulin molecule.



Synthesis of the Thyroid Hormones

- Formation and secretion of thyroglobulin. (Influenced by TSH).
- Iodide trapping (influenced by TSH).
- Oxidation of the iodide ion (peroxidase)



**The first stage in the formation of thyroid hormones is transport of iodides from the blood into the thyroid glandular cells and follicles. The basal membrane of the thyroid cell has the specific ability to pump the iodide actively to the interior of the cell. This is achieved by the action of a sodium-iodide symporter (NIS), which co-transports one iodide ion along with two sodium ions across the basolateral (plasma) membrane into the cell. The energy for transporting iodide against a concentration gradient comes from the sodium-potassium ATPase pump, which pumps sodium out of the cell, thereby establishing a low intracellular sodium concentration and a gradient for facilitated diffusion of sodium into the cell. This process of concentrating the iodide in the cell is called iodide trapping

**Iodide is transported out of the thyroid cells across the apical membrane into the follicle by a chloride-iodide ion counter-transporter molecule called pendrin. The thyroid epithelial cells also secrete into the follicle thyroglobulin that contains tyrosine amino acids to which the iodide ions will bind.

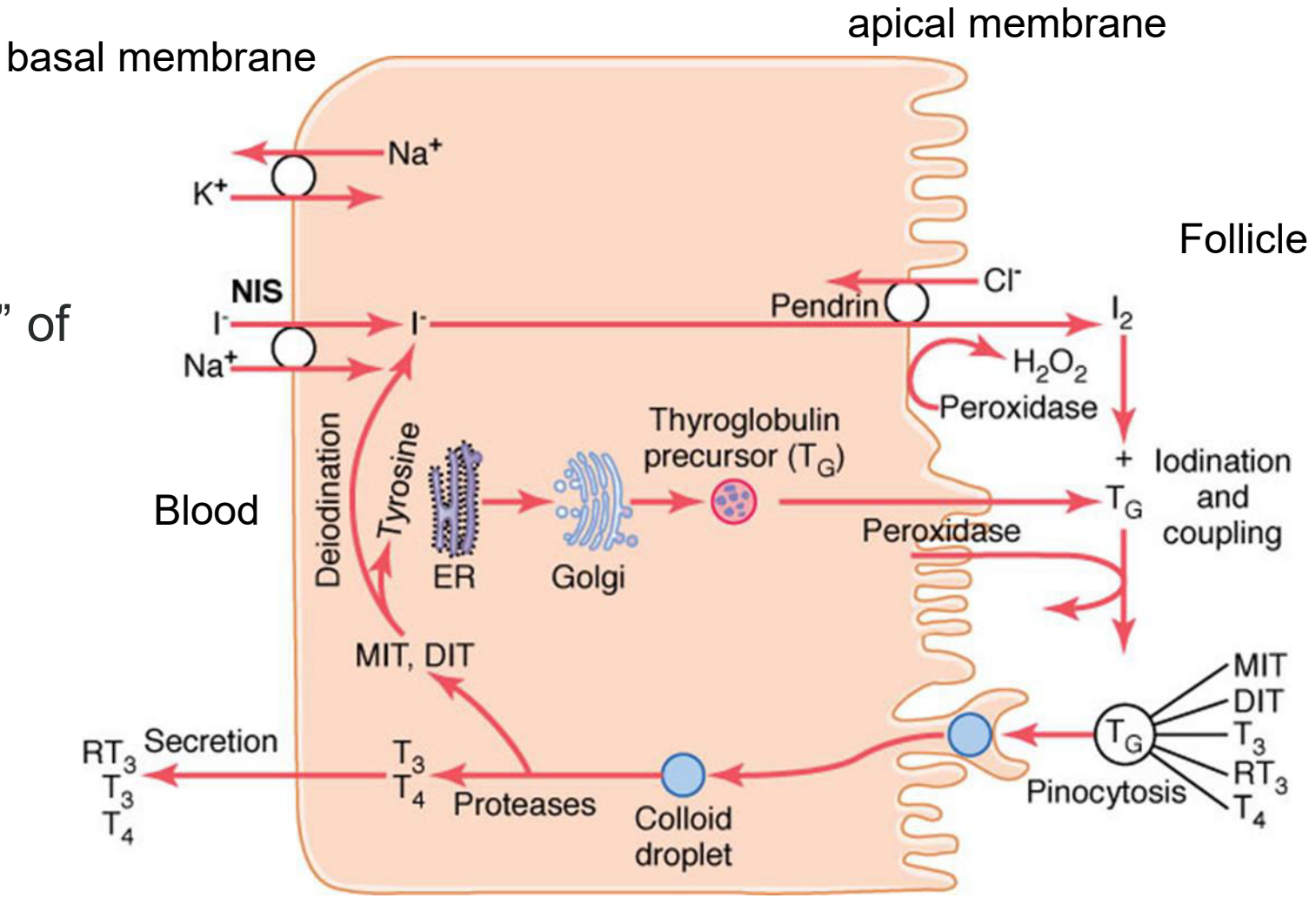
** The rate of iodide trapping by the thyroid is influenced by several factors, the most important being the concentration of TSH.

*' The first essential step in the formation of the thyroid hormones is conversion of the iodide ions to an oxidized form of iodine that is then capable of combining directly with the amino acid tyrosine. This oxidation of iodine is promoted by the enzyme peroxidase.

** When the peroxidase system is blocked or when it is hereditarily absent from the cells, the rate of formation of thyroid hormones falls to zero.

Synthesis of the Thyroid Hormones

- Iodination of tyrosine and formation of the thyroid hormones—“organification” of thyroglobulin.
- Coupling DIT, MIT



** The binding of iodine with the thyroglobulin molecule is called organification of the thyroglobulin.

** Tyrosine is first iodized to monoiodotyrosine and then to diiodotyrosine. Then, during the next few minutes, hours, and even days, more and more of the iodotyrosine residues become coupled with one another.

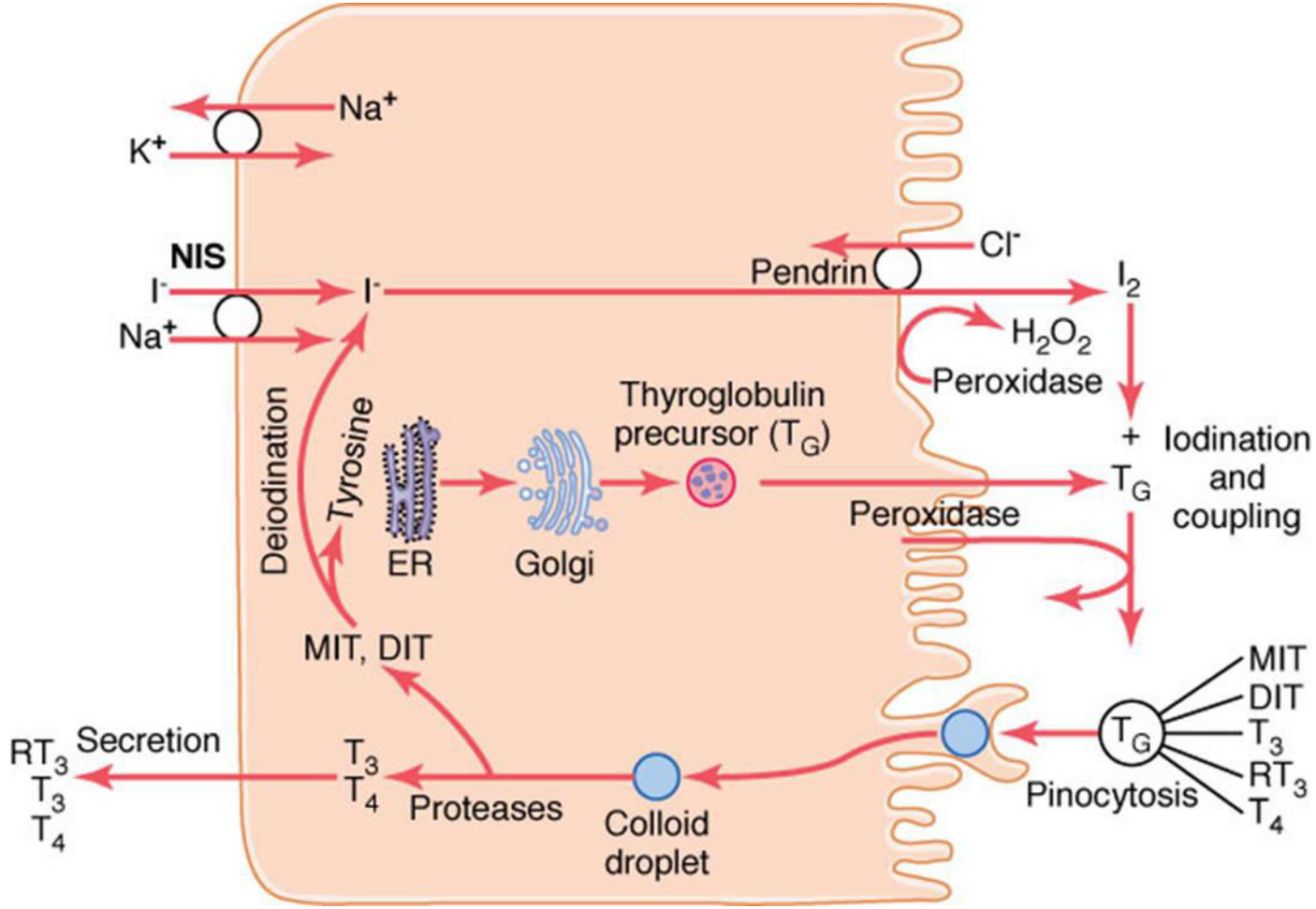
** The major hormonal product of the coupling reaction is the molecule thyroxine (T 4), which is formed when two molecules of diiodotyrosine are joined together; the thyroxine then remains part of the thyroglobulin molecule. Or one molecule of monoiodotyrosine couples with one molecule of diiodotyrosine to form triiodothyronine (T 3), which represents about one-fifteenth of the final hormones

Storage of Thyroglobulin.

- The thyroid gland is unusual among the endocrine glands in its ability to store large amounts of hormone.
- Each thyroglobulin molecule contains up to 30 thyroxine molecules and a few triiodothyronine molecules.
- This supply the body with its normal requirements of thyroid hormones for 2 to 3 months. Therefore, when synthesis of thyroid hormone ceases, the physiologic effects of deficiency are not observed for several months.

Secretion of the Thyroid Hormones

- Pinocytosis of thyroglobulin
- Proteases cleavage
- Recycling of MIT, DIT (Deiodinase)
- Secretion of T3, T4 into the blood



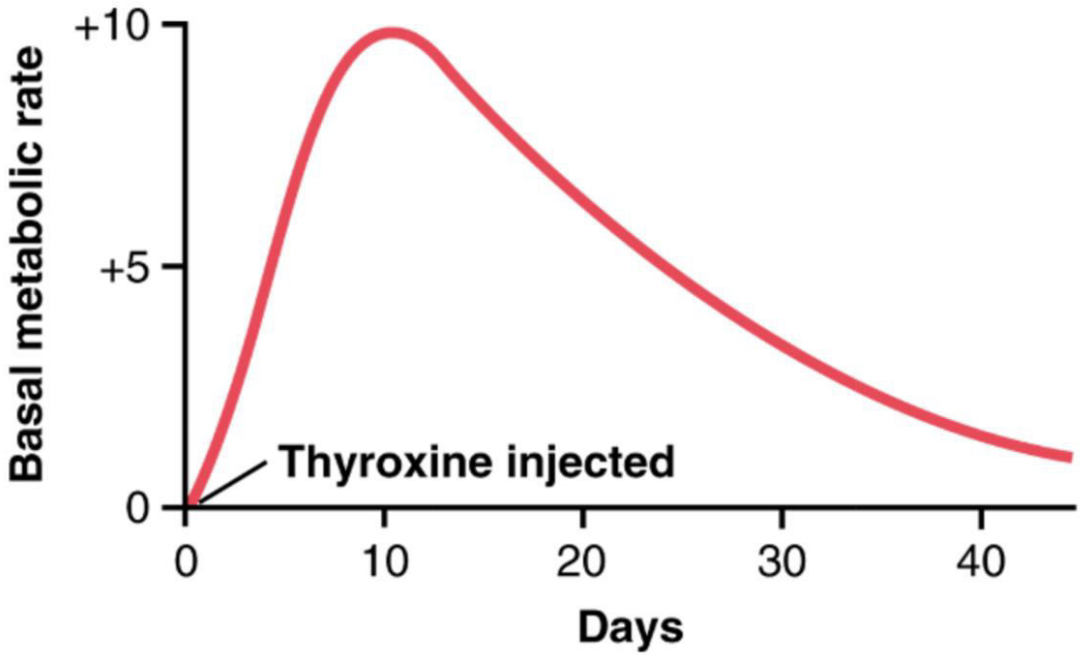
**Iodine is cleaved from MIT and DIT by a deiodinase enzyme that makes virtually all this iodine available again for recycling within the gland for forming additional thyroid hormones. Congenital absence of this deiodinase enzyme may cause iodine deficiency because of failure of this recycling process.

Transport of Thyroxine and Triiodothyronine to Tissues

- Upon entering the blood, more than 99% of the thyroxine and triiodothyronine combines immediately with plasma proteins (thyroxine-binding globulin).
- Half the thyroxine in the blood is released to the tissue cells about every 6 days. (T3 -- 1 day).
- Upon entering the tissue cells, both thyroxine and triiodothyronine again bind with intracellular proteins. (again stored).
- All the thyroxine is eventually converted to triiodothyronine in the tissues.

Thyroid Hormones Have Slow Onset and Long Duration of Action.

- long latent period before thyroxine activity begins (2—3d).
- Activity increases progressively and reaches a maximum in 10 to 12 days.
- T4 half-life (about 15 days).
- Some of the activity persists for as long as 6 weeks to 2 months.
- The actions of T3 occur about four times as rapidly as those of thyroxine.

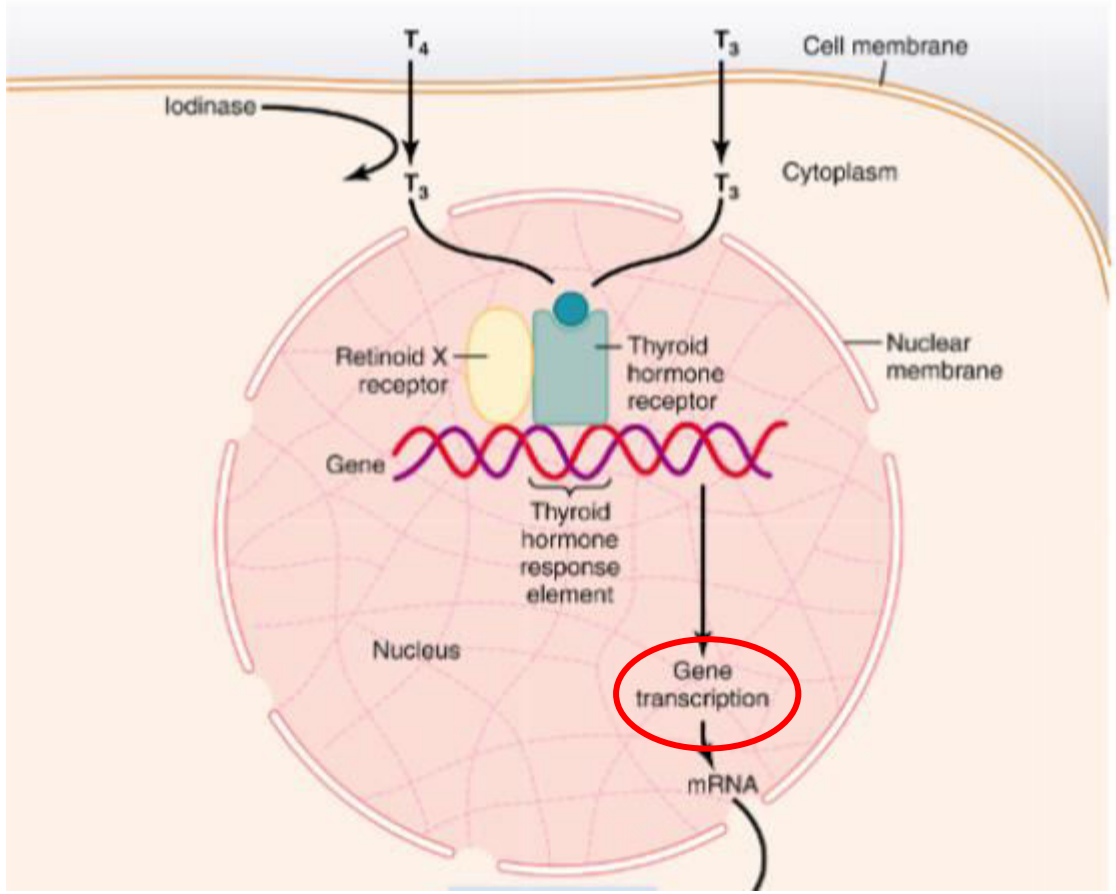


** Most of the latency and prolonged period of action of these hormones are probably caused by their binding with proteins both in the plasma and in the tissue cells, followed by their slow release. However, we shall see in subsequent discussions that part of the latent period also results from the manner in which these hormones perform their functions in the cells themselves.

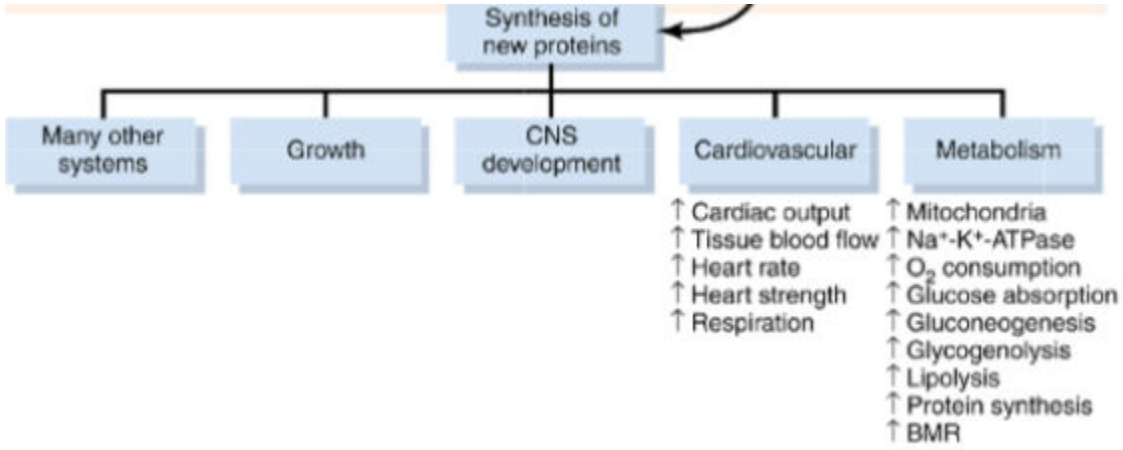
Physiological Functions of the Thyroid Hormones

CHAPTER 76

Hormones Increase the Transcription of Large Numbers of Genes



- **Thyroid hormone does not have any discrete target organs. It affects virtually every tissue in the body.**



**The general effect of thyroid hormone is to activate nuclear transcription of many genes. Therefore, in virtually all cells of the body, great numbers of protein enzymes, structural proteins, transport proteins, and other substances are synthesized. The net result is a generalized increase in functional activity throughout the body.

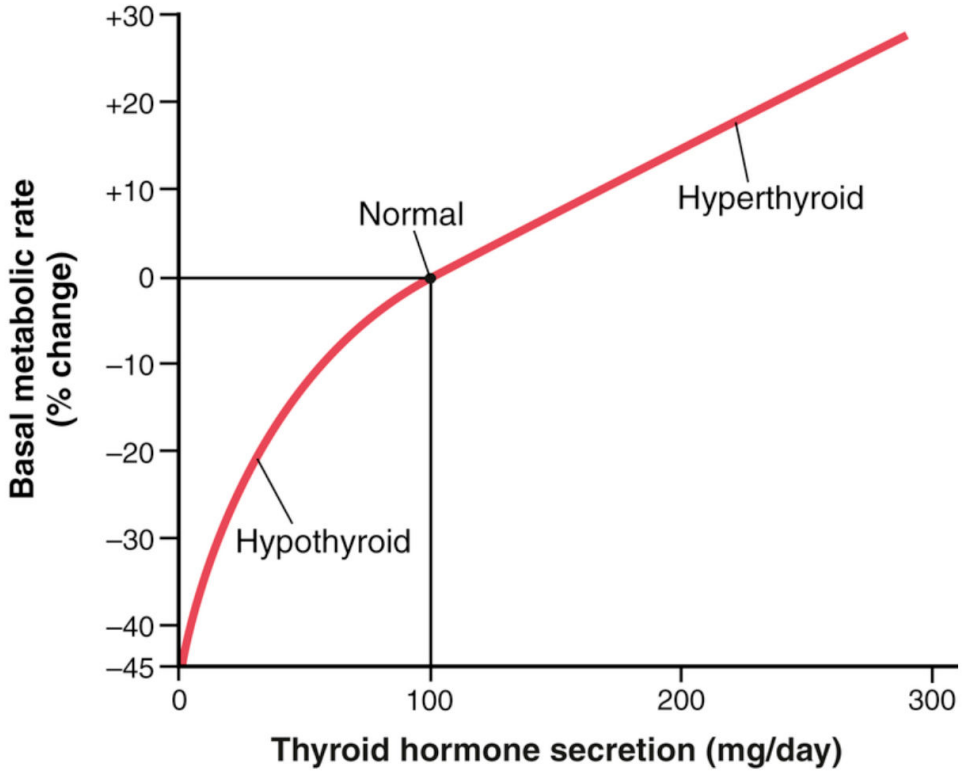
** Most of the thyroxine secreted by the thyroid is converted to triiodothyronine.

** more than 90% of the thyroid hormone that binds with the receptors is triiodothyronine.

** Thyroid hormones also appear to have nongenomic cellular effects that are independent of their effects on gene transcription.

Thyroid Hormones Increase Cellular Metabolic Activity

- Increase the number and activity of mitochondria (increased ATP production).
- Increase active transport of ions through cell membranes Na-K-ATPase.
- Increase the amount of heat.



** The basal metabolic rate can increase to 60% to 100% above normal when large quantities of thyroid hormones are secreted.

** basal metabolic rate (BMR), the rate of energy expenditure under standard or basal conditions (awake, at rest, and fasting). When BMR increases, cellular metabolism of carbohydrates, lipids, and proteins increases.

** The rate of utilization of foods for energy is greatly accelerated.

** Although the rate of protein synthesis is increased, at the same time the rate of protein catabolism is also increased.

** ** The mental processes are excited, and the activities of most of the other endocrine glands are increased.

Metabolic Effect of Thyroid Hormones

❖ Stimulation of carbohydrate metabolism

Thyroid hormone stimulates almost all aspects of carbohydrate metabolism.

❖ Stimulation of fat metabolism

- Essentially all aspects of fat metabolism are also enhanced.
- Decreases fat stores of the body.
- Increases free fatty acid concentration in the plasma.
- Decreases the concentrations of cholesterol, phospholipids, and triglycerides in the plasma.

One of the mechanisms by which thyroid hormone decreases plasma cholesterol concentration is to increase significantly cholesterol secretion in the bile and consequent loss in the feces. A possible mechanism for the increased cholesterol secretion is that thyroid hormone induces increased numbers of low-density lipoprotein receptors on the liver cells, leading to rapid removal of low-density lipoproteins from the plasma by the liver and subsequent secretion of cholesterol in these lipoproteins by the liver cells.

Thyroid Hormones Effect on Growth and the Nervous System

- Thyroid hormone not only stimulates GH secretion and increases production of IGF-I by the liver
- Promotes the effects of GH and IGF-I on the synthesis of new structural proteins and on bone growth.
- Thyroid hormone plays a crucial role in development of the nervous system in children.
- Thyroid hormone is also essential for normal CNS activity in adults.

**nervous system: They promote synapse formation, myelin production, and growth of dendrites.

**Thyroid-deficient children have stunted growth that can be reversed by thyroid replacement therapy, but excess thyroid hormone does not produce excessive growth.
** In children with hyperthyroidism, excessive skeletal growth often occurs, causing the child to become considerably taller at an earlier age. However, the bones also mature more rapidly and the epiphyses close at an early age, so the duration of growth and the eventual height of the adult actually may be shortened.

**An important effect of thyroid hormone is to promote growth and development of the brain during fetal life and for the first few years of postnatal life. If the fetus does not secrete sufficient quantities of thyroid hormone, growth and maturation of the brain both before birth and afterward are greatly retarded and the brain remains smaller than normal. Without specific thyroid therapy within days or weeks after birth, the child without a thyroid gland will remain mentally deficient throughout life

Sympathomimetic Effect

- Thyroid hormone increases target-cell responsiveness to catecholamines.
- Thyroid hormone accomplishes this permissive action by causing a proliferation of catecholamine target-cell receptors.

Effect of Thyroid Hormones

- Thyroid hormone increases heart rate and force of contraction, thus increasing cardiac output.
- Increased respiration.
- Increased gastrointestinal motility.
- Effect on the function of the muscles (vigorous, tremor).
- Increases the rates of secretion of several other endocrine glands, but it also increases the need of the tissues for the hormones. (pancreases, ant. pituitry, parathyroid)

** CVS via both its direct effect on the heart, and through its effect of increasing the heart's responsiveness to catecholamines.

** slight increase in thyroid hormone usually makes the muscles react with vigor but, with excessive thyroid hormone, the muscles become weakened because of excess protein catabolism. Conversely, lack of thyroid hormone causes the muscles to become sluggish, and they relax slowly after a contraction.

Actions of Thyroid Hormones