

# The Thyroid Gland: Function and Regulation

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# Thyroid Hormones

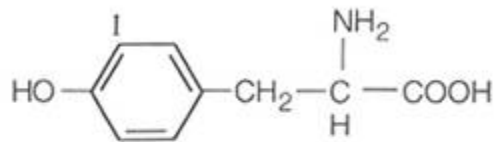
- The thyroid gland is located immediately below the larynx on each side of and anterior to the trachea.
- It is one of the largest of the endocrine glands, normally weighing 15 to 20 grams in adults.
- The thyroid secretes two major hormones, *thyroxine* and *triiodothyronine*, commonly called  $T_4$  and  $T_3$ .
- Both of these hormones profoundly increase the metabolic rate of the body.
- Thyroid secretion is controlled primarily by *thyroid-stimulating hormone (TSH)* secreted by the anterior pituitary gland.

# Thyroid Hormones

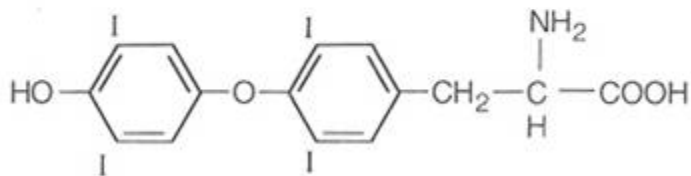
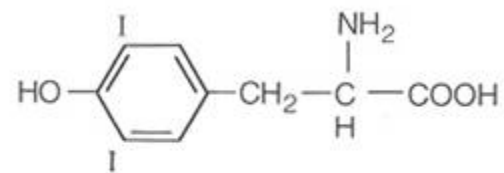
- About 93 per cent of the metabolically active hormones secreted by the thyroid gland is *thyroxine*, and 7 per cent *triiodothyronine*.
- Thyroxine is eventually converted to triiodothyronine in the tissues.
- Triiodothyronine is about four times as potent as thyroxine, but it is present in the blood in much smaller quantities and persists for a much shorter time than does thyroxine.

# Thyroid Hormones

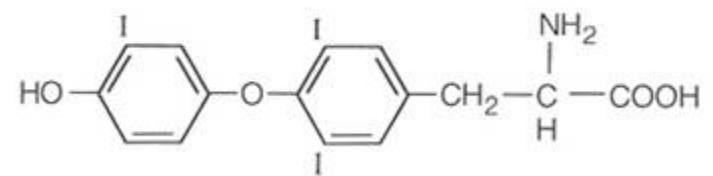
Moniodotyrosine (MIT)



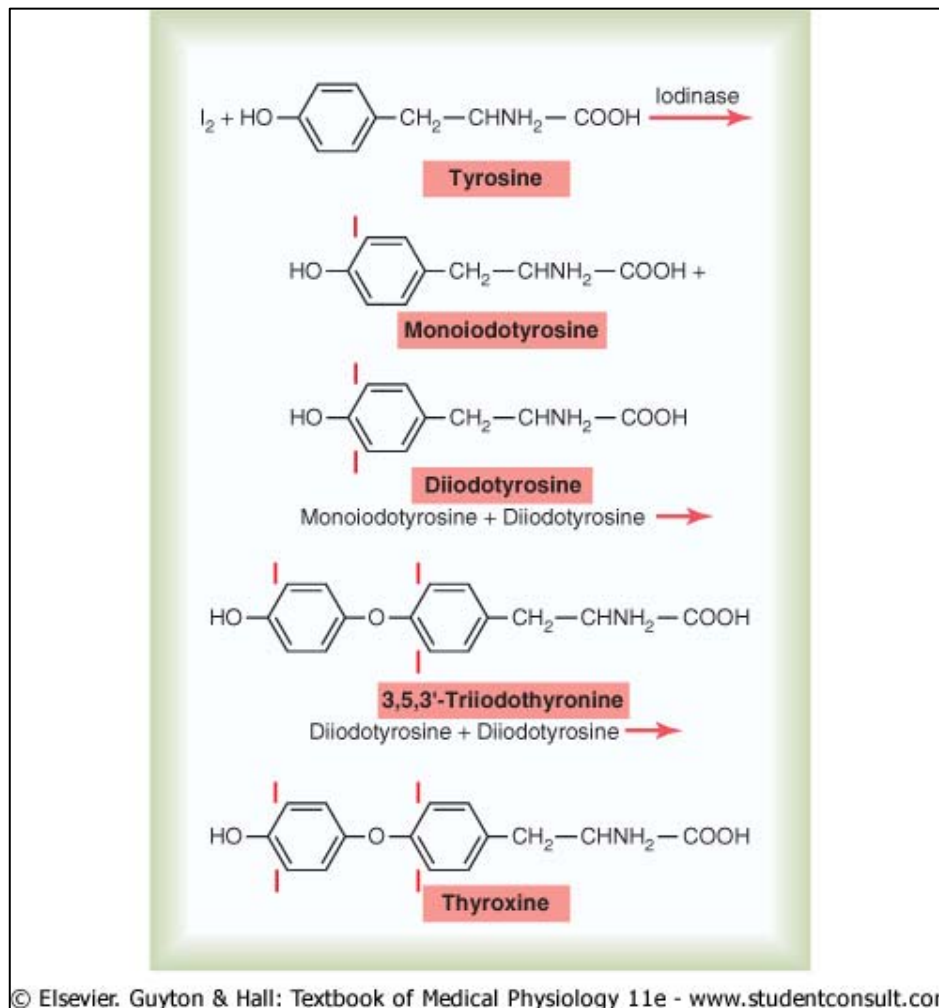
Diiodotyrosine (DIT)



3,5,3',5' - Tetraiodothyronine (L-thyroxine) (T<sub>4</sub>)



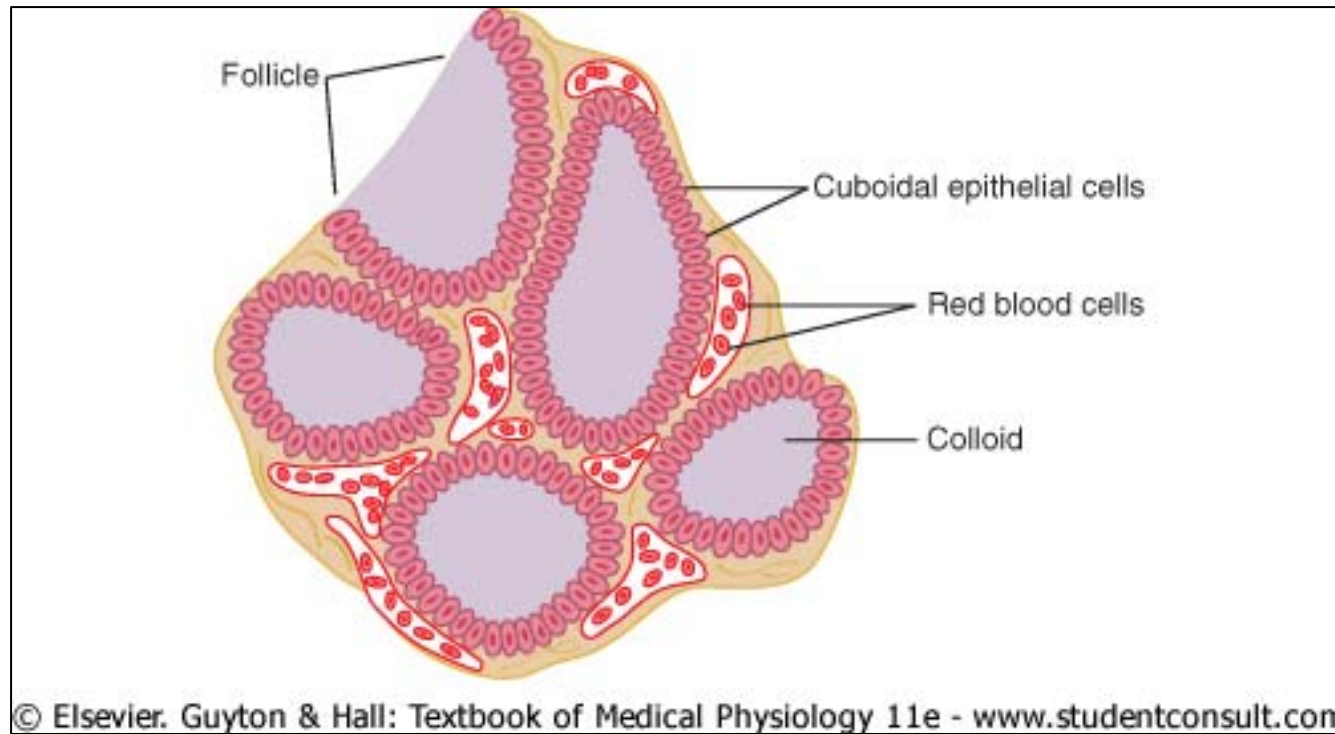
3,5,3' - Triiodothyronine (T<sub>3</sub>)



Chemistry of thyroxine and triiodothyronine formation.

# Thyroid Hormone Synthesis

- Large numbers of closed *follicles* (100 to 300 micrometers in diameter) are filled with a secretory substance called *colloid*.
- The major constituent of colloid is the large glycoprotein *thyroglobulin*, with a molecular weight of about 335,000 per subunit. Each Tg exists as a homodimer with a molecular weight of 660,000.
- The endoplasmic reticulum and Golgi apparatus synthesize and secrete the thyroglobulin into the follicles.
- Thyroglobulin contains the thyroid hormones, T<sub>3</sub> and T<sub>4</sub>, within its molecule.



Microscopic appearance of the thyroid gland, showing location of thyroglobulin in the follicles.

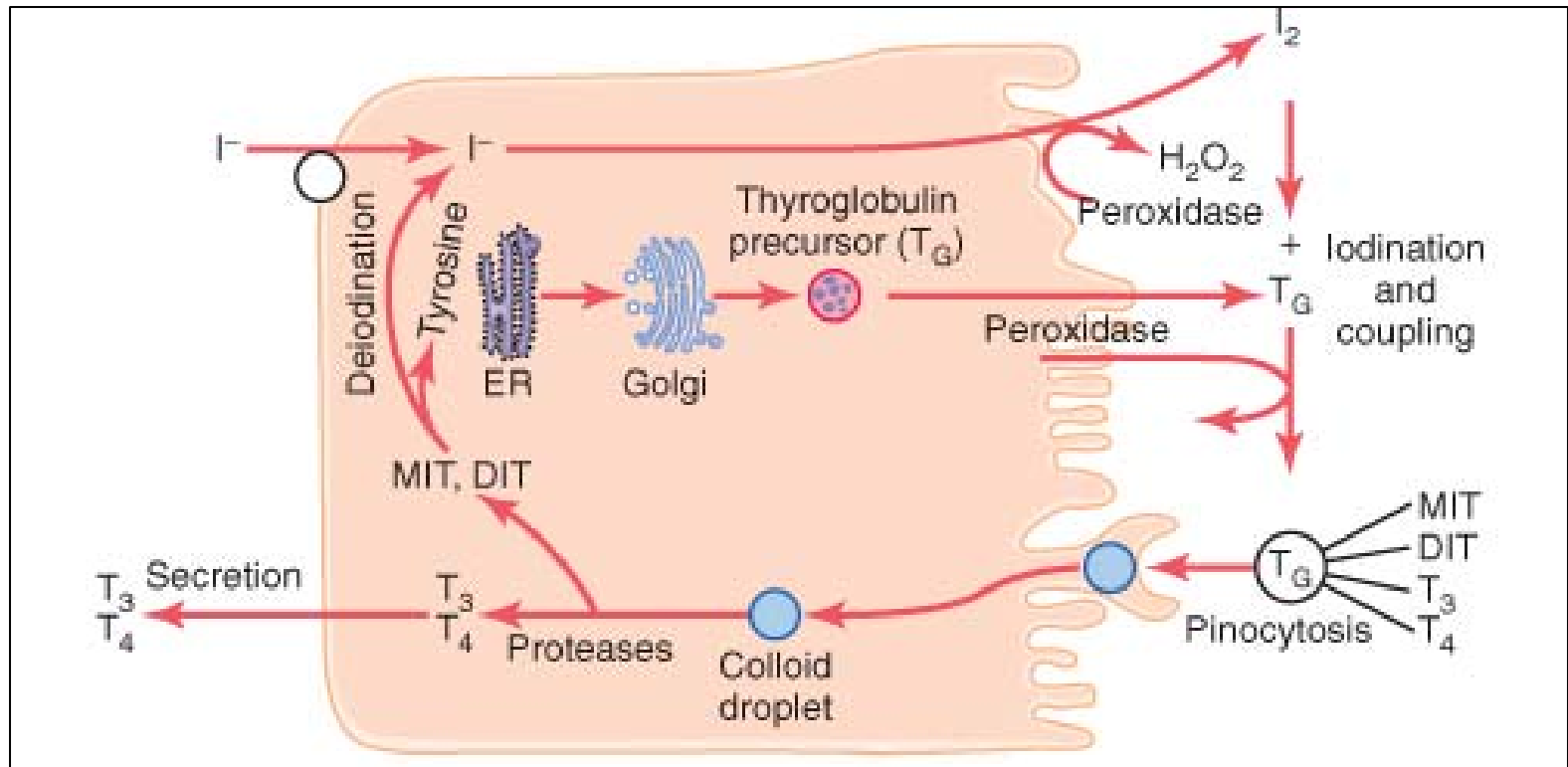
# Iodine

- To form normal quantities of thyroxine, about 50 milligrams of ingested iodine in the form of iodides are required *each year*, or about *1 mg/week*.
- Iodides ingested orally are absorbed from the gastrointestinal tract.
- Iodine is removed from the circulating blood by the cells of the thyroid gland and used for synthesis of the thyroid hormones.
- The basal membrane of the thyroid cell has the specific ability to pump the iodide actively to the interior of the cell, using a pump called the sodium-iodide symporter (NIS). This is called *iodide trapping*. In a normal gland, the iodide pump concentrates the iodide to about 30 times its concentration in the blood.



# Thyroid Hormone Synthesis

- Iodine uptake:  $\text{Na}^+$  (2) /  $\text{I}^-$  (1) symporter (NIS),  $\text{Na}^+$  (3)/ $\text{K}^+$  (2)ATPase
- Thyroidal peroxidase (TPO)
  - Oxidation of  $\text{I}^-$  to  $\text{I}_2$  ( $\text{H}_2\text{O}_2$  required)
  - Iodination of tyrosyl residues in thyroglobulin
  - Coupling of MIT and DIT
- Endocytosis of iodinated Tg
- Lysosomal cleavage of  $\text{T}_3$  and  $\text{T}_4$
- *Defects in organification and synthesis can lead to goiter and hypothyroidism*



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Thyroid cellular mechanisms for iodine transport, thyroxine and triiodothyronine formation, and thyroxine and triiodothyronine release into the blood. MIT, monoiodotyrosine; DIT, diiodotyrosine;  $T_3$ , triiodothyronine;  $T_4$ , thyroxine; TG, thyroglobulin.

# Thyroid Hormone Synthesis

- 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.
- Iodination of the tyrosines in thyroglobulin takes place within the colloid.

# Thyroid Hormone Synthesis

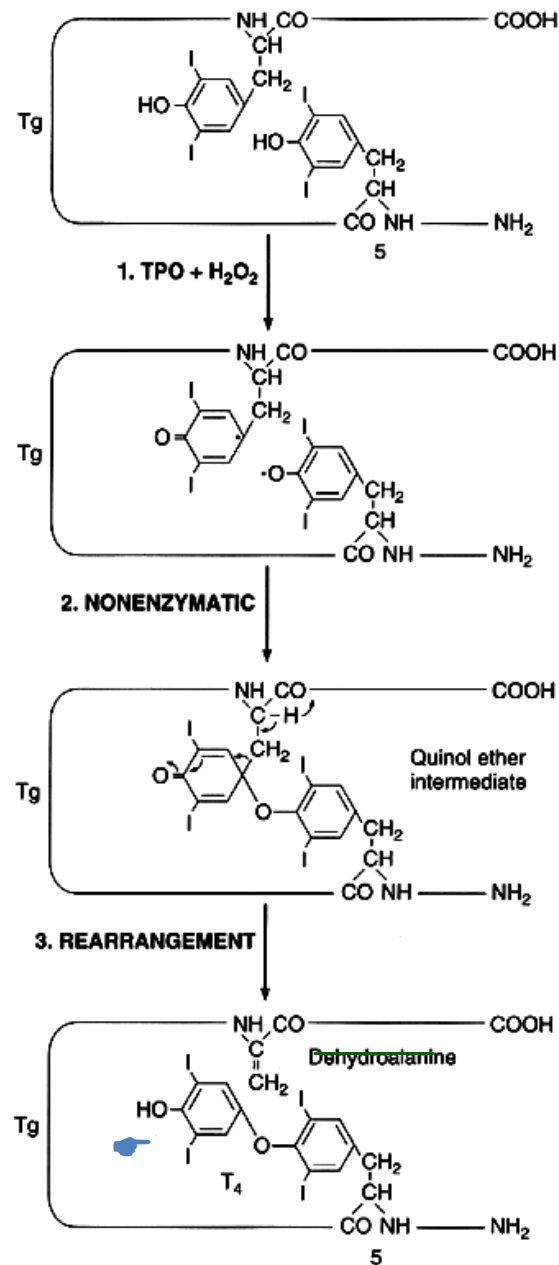
- Each molecule of thyroglobulin contains about 130 tyrosine amino acids, and they are the major substrates that combine with iodine to form the thyroid hormones. Thus, the thyroid hormones form *within* the thyroglobulin molecule.
- Each thyroglobulin molecule contains up to 30 iodinated tyrosine molecules, but only 3 thyroxines and even fewer triiodothyronines.
- In this form, the thyroid hormones are stored in the follicles in an amount sufficient to supply the body with its normal requirements of thyroid hormones for 2 to 3 months.

# Coupling

Coupling takes place within the thyroglobulin (Tg) molecule.

The  $H_2O_2$  is produced by two enzymes, Duox 1 and Duox 2.

The final product consists of two linked iodinated tyrosine residues.  
 $MIT + DIT = T_3$   
 $DIT + DIT = T_4$



134 Y residues

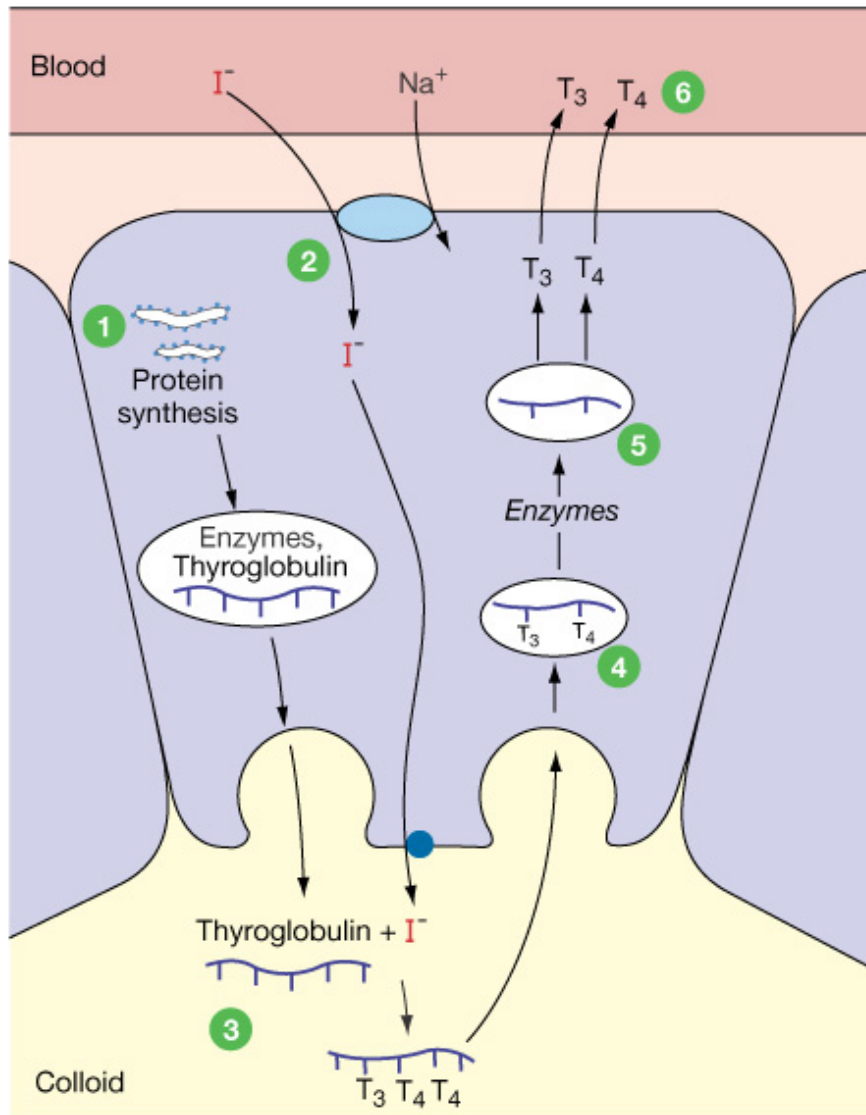
25-30 are iodinated

3 T<sub>4</sub> per Tg

1 T<sub>3</sub> per 5 Tg

Tg = thyroglobulin

# Thyroxine and its precursors:



- 1** Follicular cell synthesizes enzymes and thyroglobulin for colloid.
- 2** I<sup>-</sup> is co-transported into the cell with Na<sup>+</sup> and transported into colloid.
- 3** Enzymes add iodine to thyroglobulin to make T<sub>3</sub> and T<sub>4</sub>.
- 4** Thyroglobulin is taken back into the cell.
- 5** Intracellular enzymes separate T<sub>3</sub> and T<sub>4</sub> from the protein.
- 6** Free T<sub>3</sub> and T<sub>4</sub> enter the circulation.

Figure 23-9: Thyroid hormone synthesis

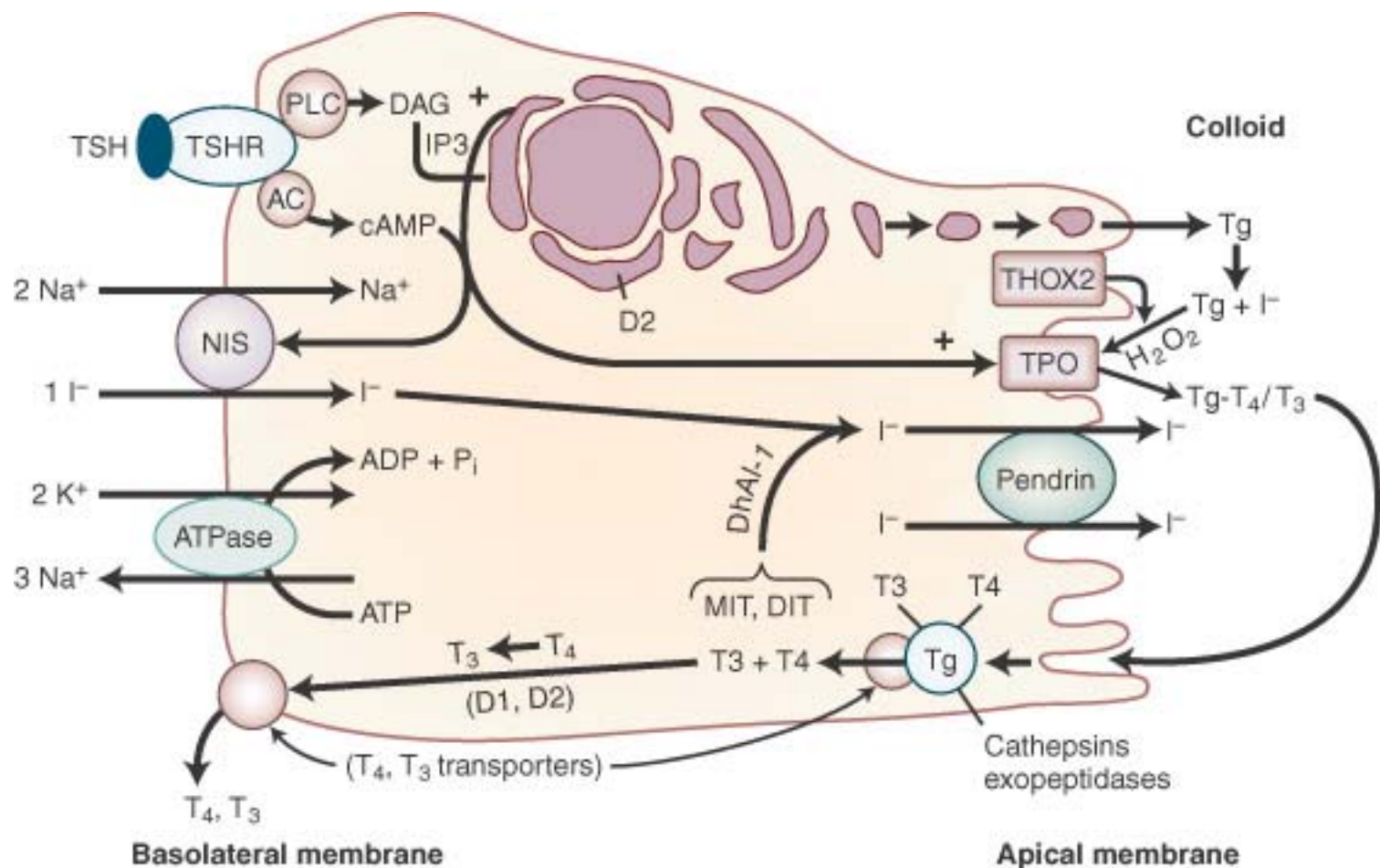
# Thyroid Hormone Synthesis

- Thyroxine and triiodothyronine must first be cleaved from the thyroglobulin molecule, and then these free hormones are released.
- *Pinocytosis* occurs bringing the thyroglobulin from the colloid into the cells.
- The pinocytic vesicle combines with *lysosomes* to release the contents.
- *Proteases* then cleave the thyroglobulin molecule adjacent to the tyrosine residues.
- Monoiodotyrosine and diiodotyrosine are also cleaved out of the thyroglobulin.

# Thyroid Hormone Synthesis

- The iodine is cleaved from the monoiodotyrosine and diiodotyrosine by a *deiodinase enzyme* that makes virtually all this iodine available again for recycling within the gland for forming additional thyroid hormones.
- In the congenital absence of this deiodinase enzyme, many persons become iodine-deficient because of failure of this recycling process.





**Figure 10–2.** Schematic illustration of a follicular cell showing the key aspects of thyroid iodine transport and thyroid hormone synthesis. *NIS*, Sodium-iodide symporter; *T<sub>3</sub>*, triiodothyronine; *T<sub>4</sub>*, thyroxine; *Tg*, thyroglobulin; *TPO*, thyroid peroxidase *TSHR*, thyrotropin receptor.

(Modified from Spitzweg C, Heufelder AE, Morris JC. Thyroid iodine transport. *Thyroid* 2000;10(4):321-330.)

# Thyroid Hormone Release and Transport

- About 93 per cent of the thyroid hormone released from the thyroid gland is normally thyroxine and only 7 per cent is triiodothyronine. However, during the ensuing few days, about one half of the thyroxine is slowly deiodinated to form additional triiodothyronine.
- T3 and T4 combine mainly with *thyroxine-binding globulin* and much less so with *thyroxine-binding prealbumin (transthyretin)* and *albumin*.

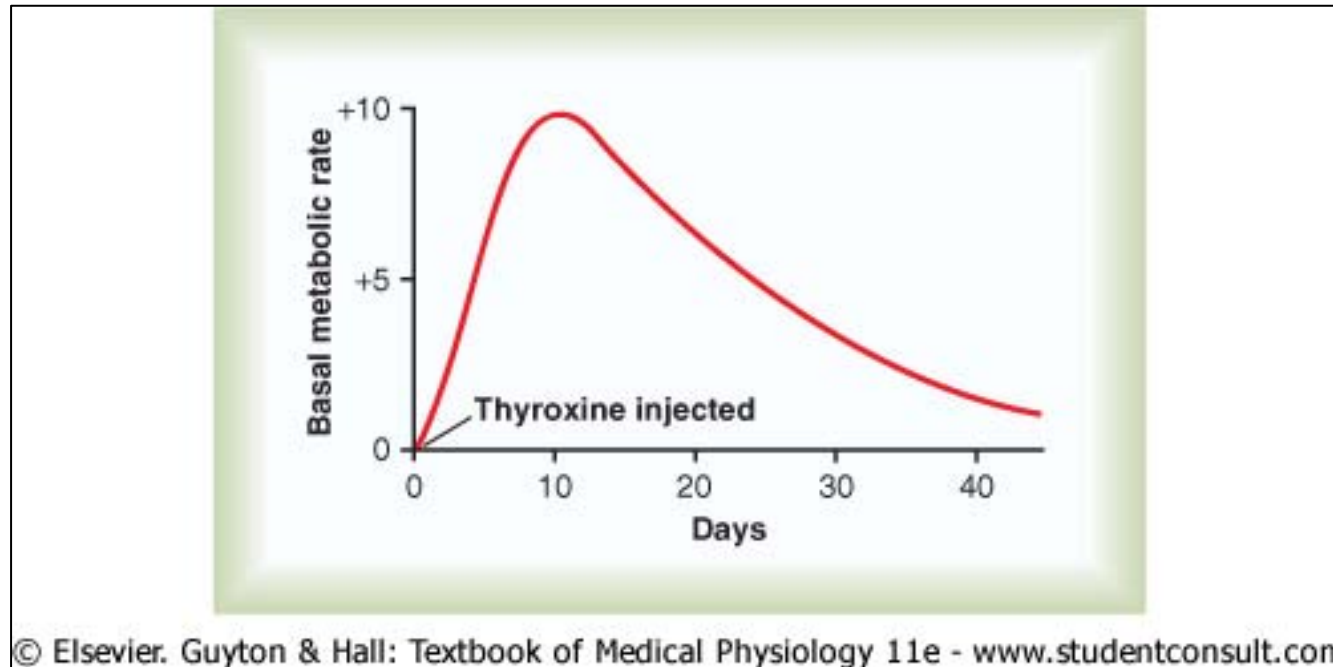
# Thyroid Hormone Transport

- Binding to carrier proteins allows for even distribution of hydrophobic entities throughout the circulation.
- The free fraction is the major determinant of:
  - Amount available to cells
  - Rate of hormone turnover
  - Metabolic state of the individual
  - Thyroid axis regulation
- *Hepatic failure and nephrotic syndrome*

# Thyroid Hormone Concentration

- The concentration of thyroid hormones inside the cell is 2-3 fold that seen in the plasma.
- Transport into cells is mediated by a family of energy-dependent transporters and some of them are cell-type specific. T3 and T4 normally do not compete for uptake.
- On entering the tissue cells, both thyroxine and triiodothyronine again bind with intracellular proteins.
- Proteins that bind T4 and T3 are present in the cytosol and nucleus.
- Nuclear to cytosol ratios are 50:1 to 250:1.

## Thyroid Hormones Have Slow Onset and Long Duration of Action.



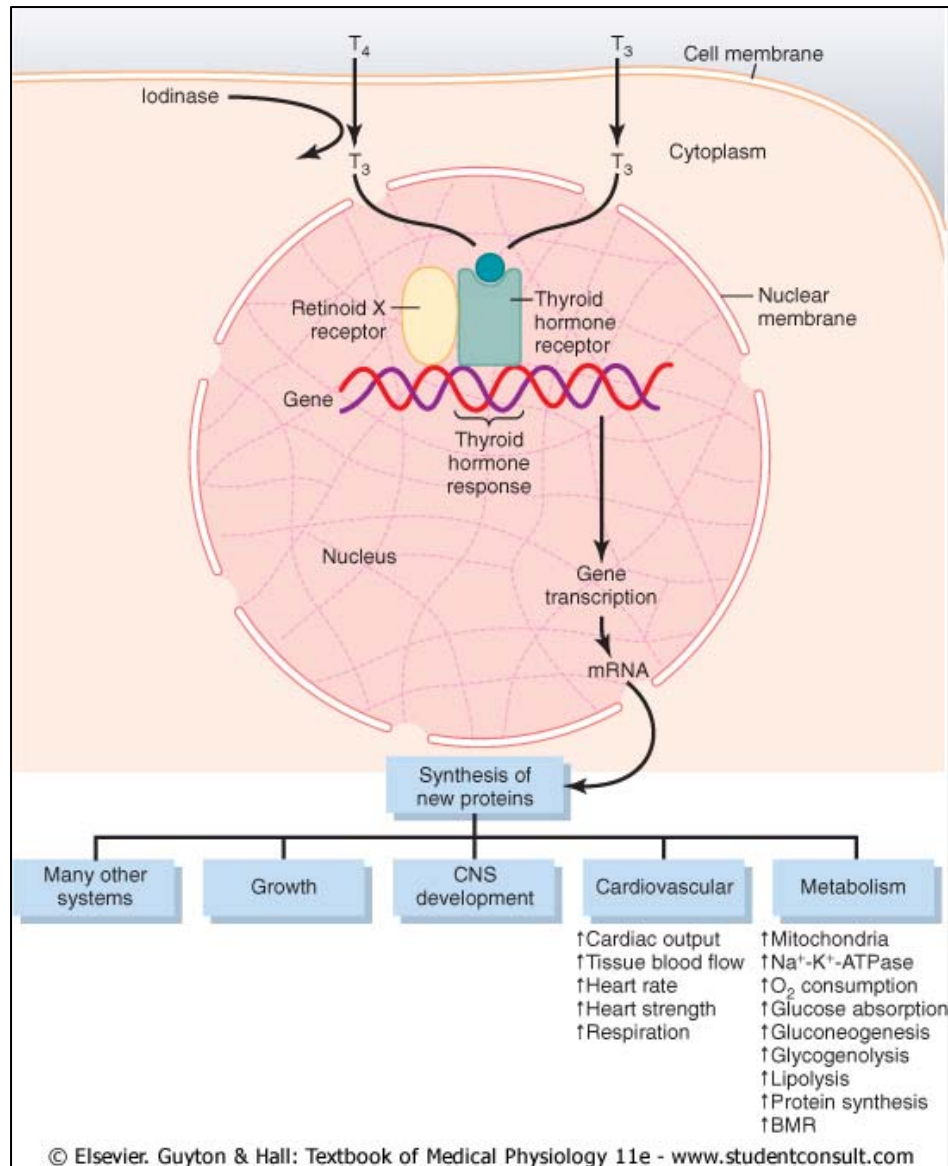
Effect on the basal metabolic rate caused by administering a single large dose of thyroxine.

# Thyroid Hormone Receptor

- Is a nuclear receptor.
- Binding of T3 to a gene that is **positively regulated**, such as TPO, initiates a conformational change such that one or more repressors of transcription are dissociated and replaced by coactivators such as histone acetyltransferase, increasing transcription.
- **Negative regulation**, as is seen for TRH gene transcription, may involve specific negative TREs. Coactivator and histone acetylation activating proteins dissociate as a result of TR-T3 binding.

# Thyroid Hormone Receptors

- There are two thyroid hormone receptor genes, A and B.
- In general, feedback regulation and cochlear development are functions of TR $\beta$  and cardiac functions and energy metabolism are regulated by TR $\alpha$ .
- Differences in the ligand binding domains of TR $\alpha$  and TR $\beta$  will allow for design of thyroid hormone analogs selective for one receptor subtype.
- *Potential clinical applications include selective suppression of TSH in thyroid cancer with agonist specific for the beta form.*

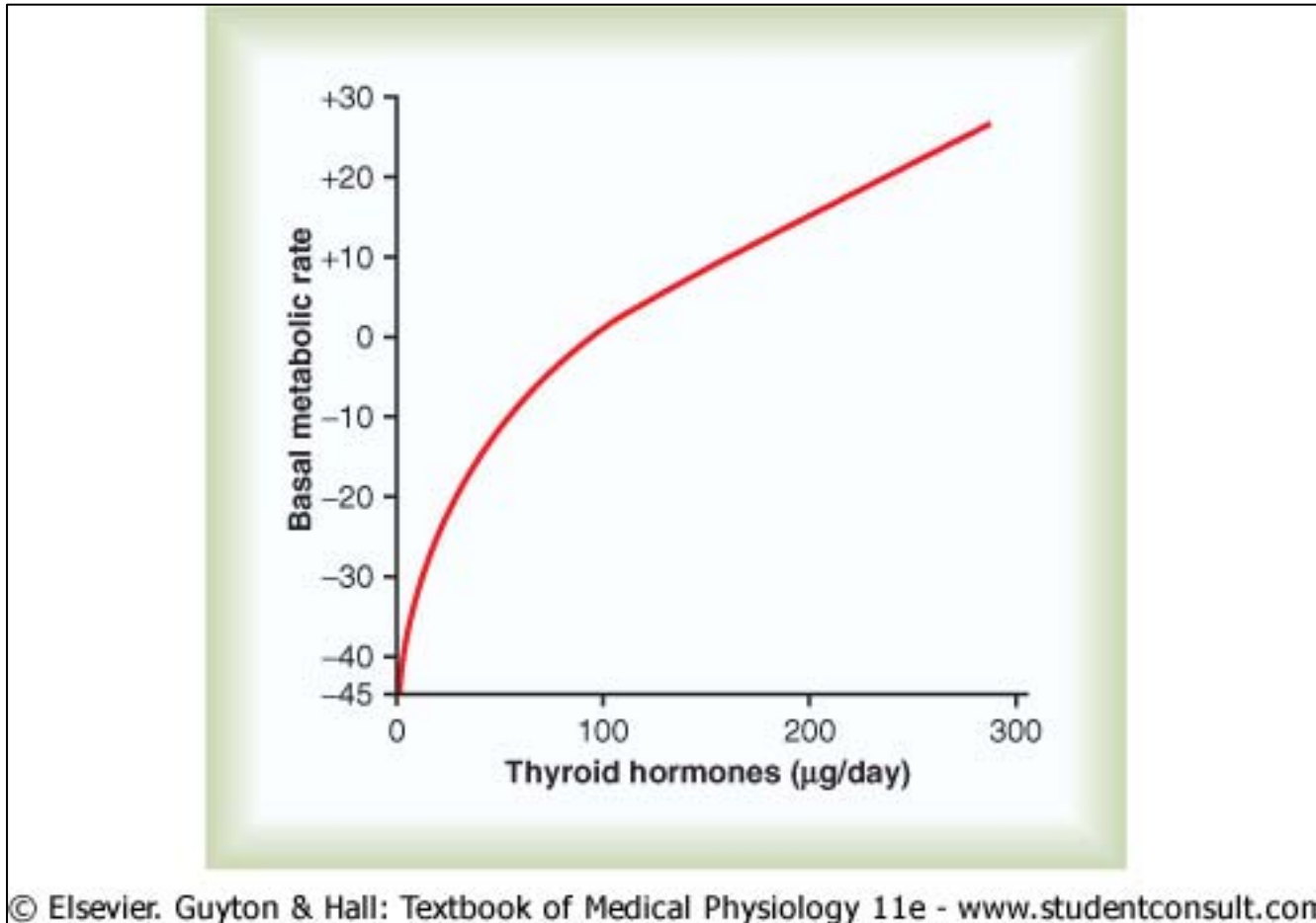


Thyroid hormone activation of target cells.



# Thyroid Hormone Actions

- The general effect of thyroid hormone is to activate nuclear transcription of large numbers of genes
- Therefore, in virtually all cells of the body, great numbers of protein enzymes, structural proteins, transport proteins, and other substances are synthesized.
- The thyroid hormone receptor usually forms a heterodimer with *retinoid X receptor (RXR)* and binds at specific *thyroid hormone response* elements on the DNA.
- This hormone receptor complex then initiates the transcription of many genes.
- The thyroid hormones increase the metabolic activities of almost all the tissues of the body.



Approximate relation of daily rate of thyroid hormone (T4 and T3) secretion to the basal metabolic rate.

# Physiological Effects of Thyroid Hormones

- The rate of utilization of foods for energy is greatly accelerated.
- Protein synthesis is greatly increased as well as the rate of protein catabolism.
- The mitochondria in most cells of the animal's body increase in size as well as number. Furthermore, the total membrane surface area of the mitochondria increases almost directly in proportion to the increased metabolic rate of the whole animal.

# Physiological Effects of Thyroid Hormones

- The growth rate of young people is greatly accelerated.
- Growth and development of the brain during fetal life and for the first few years of postnatal life require thyroid hormones.

# Physiological Effects of Thyroid Hormones

- **Stimulation of Carbohydrate Metabolism**
- **Stimulation of Fat Metabolism**
  - *Decreases* the concentrations of cholesterol, phospholipids, and triglycerides.
  - Increases numbers of low-density lipoprotein receptors on the liver cells, leading to rapid removal of low-density lipoproteins from the plasma.
  - Increases significantly the rate of cholesterol secretion in the bile and consequent loss in the feces.

# Physiological Effects of Thyroid Hormones

- Increased metabolism in the tissues causes more rapid utilization of oxygen than normal and release of greater than normal quantities of metabolic end products from the tissues. These effects cause vasodilation in most body tissues, thus increasing blood flow.
- Cardiac output also increases.
- Thyroid hormone has a direct effect on the excitability of the heart, which in turn increases the heart rate.

# Physiological Effects of Thyroid Hormones

- Increase the strength of the heart when only a slight excess of thyroid hormone is secreted.
- However, when thyroid hormone is increased markedly, the heart muscle strength becomes depressed because of long-term excessive protein catabolism.
- The increased rate of metabolism increases the utilization of oxygen and formation of carbon dioxide; these effects activate all the mechanisms that increase the rate and depth of respiration.

# CNS Effects of Thyroid Hormones

- Excitatory effects on the central nervous system, including cognition.
- Slight increase in thyroid hormone usually makes the muscles react with vigor, but when the quantity of hormone becomes excessive, the muscles become weakened because of excess protein catabolism.
- One of the most characteristic signs of hyperthyroidism is a fine muscle tremor.
- Because of the excitable effects of thyroid hormone on the synapses, it is difficult to sleep, in case of excess.



# Effects of Thyroid Hormones

- Increases both the rates of secretion of the digestive juices and the motility of the gastrointestinal tract.
- Increases the rates of secretion of most other endocrine glands
  - insulin
  - parathyroid hormone
- Lack of thyroid hormone is likely to cause loss of libido in both males and females.
- In females lack or excess can cause menstrual irregularities.

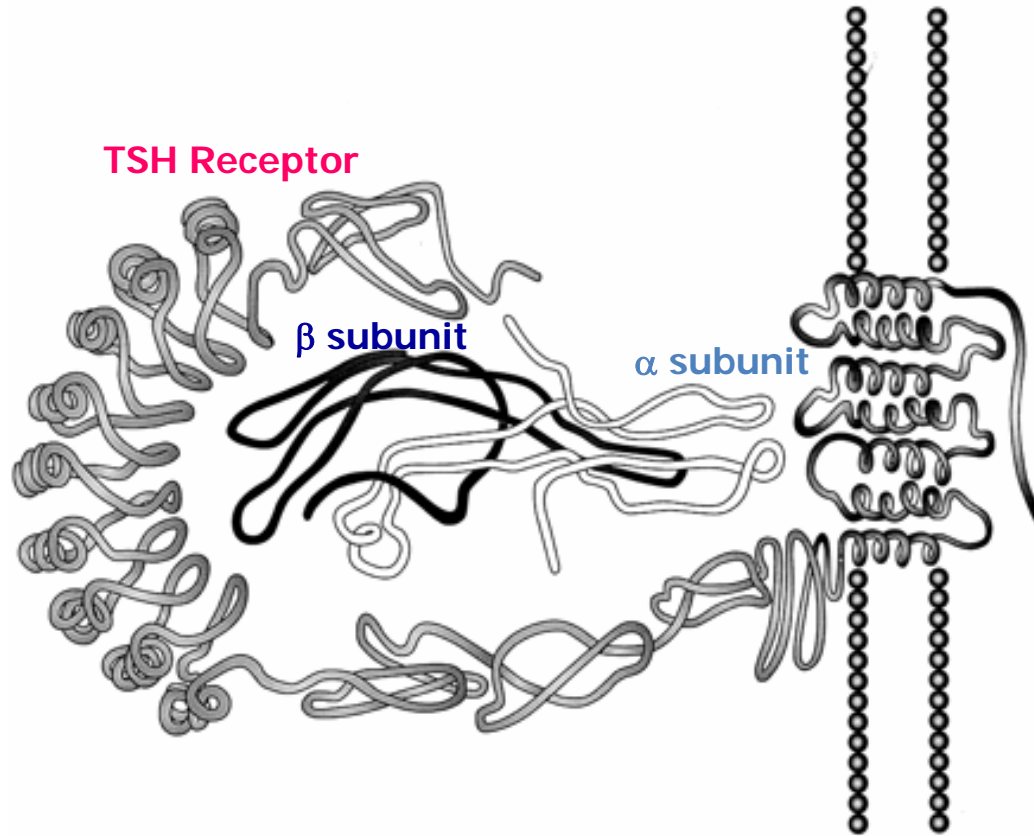
# Regulation of Thyroid Hormone Secretion

- To maintain normal levels of metabolic activity in the body, precisely the right amount of thyroid hormone must be secreted at all times
- TSH, also known as *thyrotropin*, is an anterior pituitary hormone, a glycoprotein with a molecular weight of about 28,000.
- The most important early effect after administration of TSH is to initiate proteolysis of the thyroglobulin, which causes release of thyroxine and triiodothyronine into the blood within 30 minutes.

# Regulation of Thyroid Hormone Secretion

- TSH binds with specific TSH receptors on the basal membrane surfaces of the thyroid cell.
- Most, if not all, of its effects result from activation of the "second messenger" *cyclic adenosine monophosphate (cAMP)* system of the cell.

# TSH-TSHR Complex



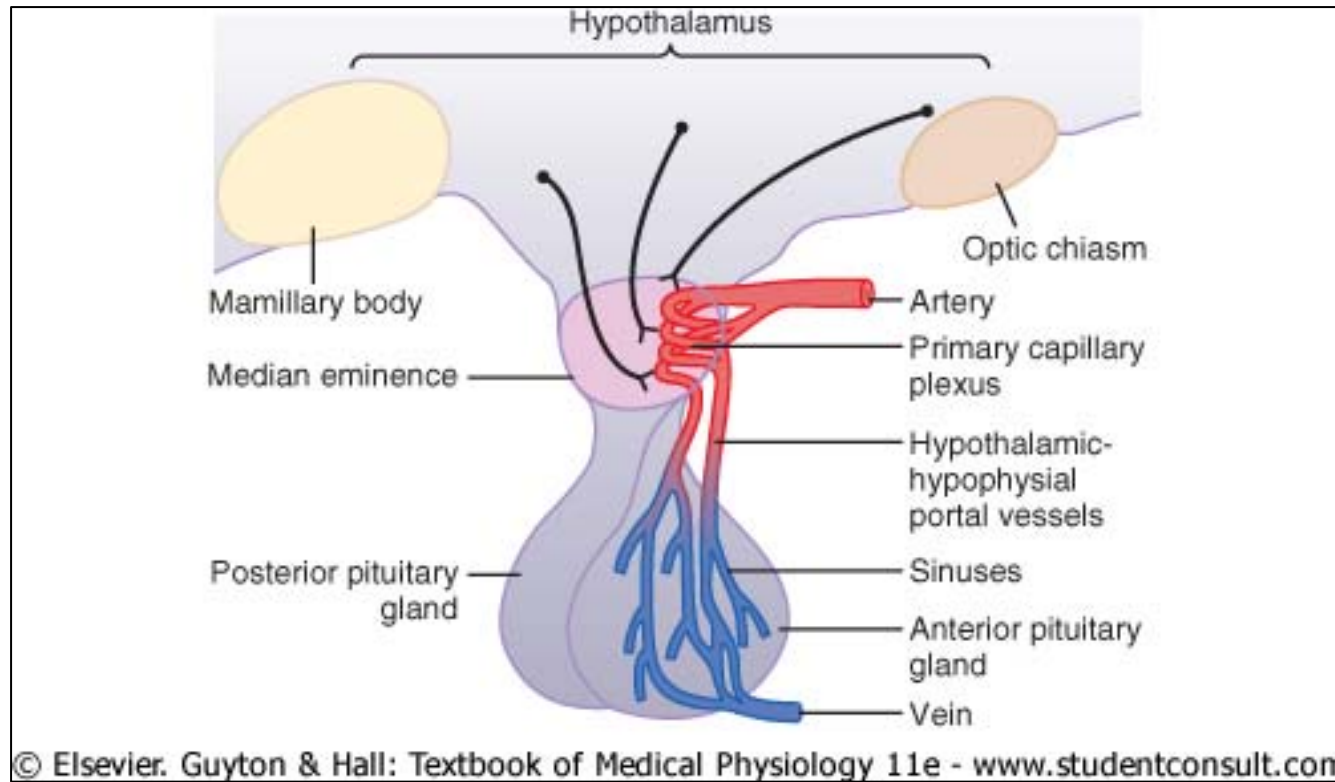
# TSH Actions

## TSH stimulates

- Thyroid growth
- Transcription of Tg
- Iodination of tyrosine
- Deiodination of T<sub>4</sub> to T<sub>3</sub>
- Lysosomal activity and TH secretion
- Thyroid iodide trap (NIS)
- Thyroid peroxidase mRNA
- Thyroid metabolism
  - Glucose uptake
  - O<sub>2</sub> consumption
  - Glucose oxidation
  - Phospholipid turnover
  - DNA/RNA synthesis

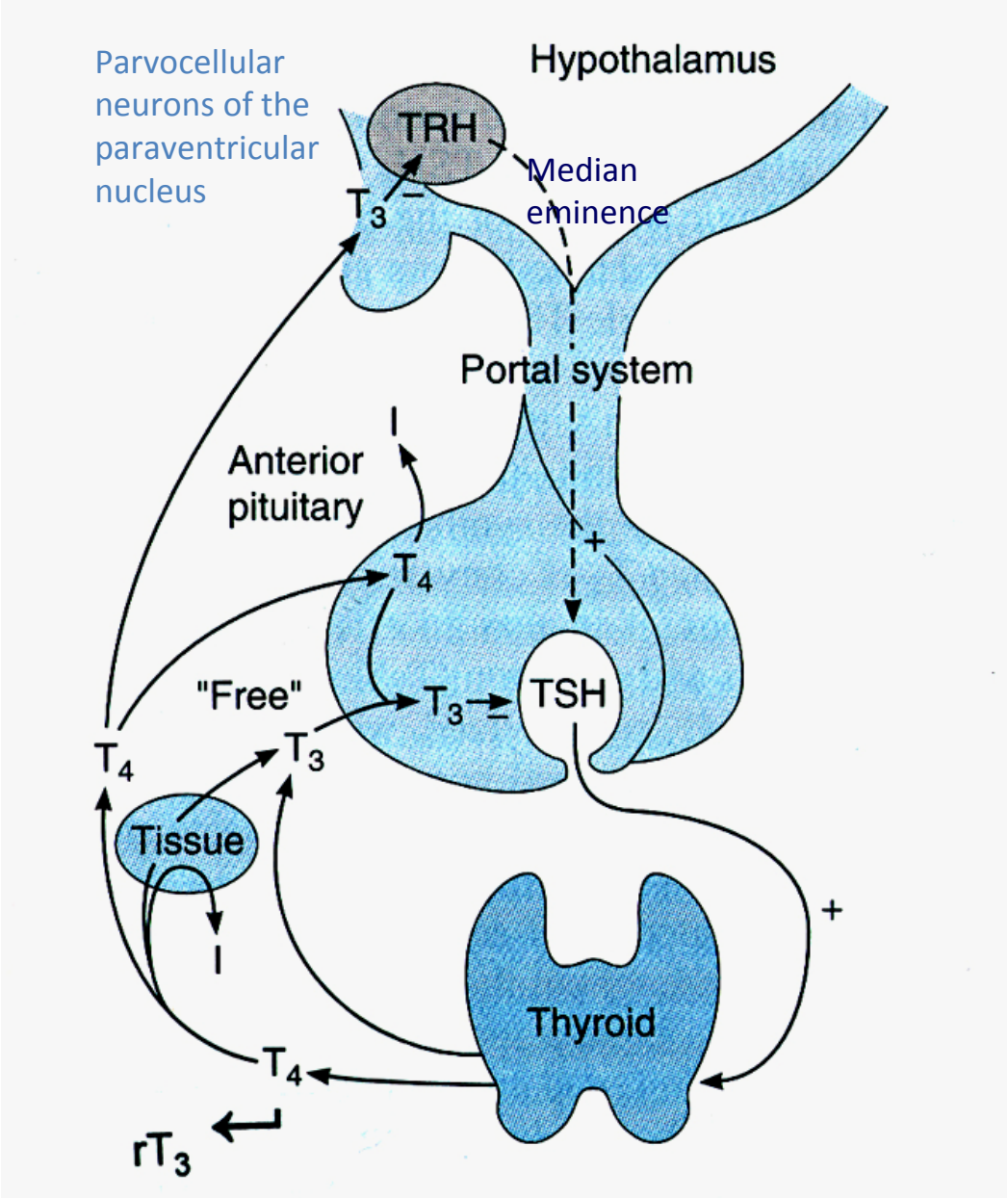
# Thyroid Axis

- Anterior pituitary secretion of TSH is controlled by a hypothalamic hormone, *thyrotropin-releasing hormone (TRH)*, which is secreted by nerve endings in the median eminence of the hypothalamus.
- From the median eminence, the TRH is then transported to the anterior pituitary by way of the hypothalamic-hypophysial portal blood
- TRH directly affects the anterior pituitary gland cells to increase their output of TSH.



## Hypothalamic-hypophysial portal system.

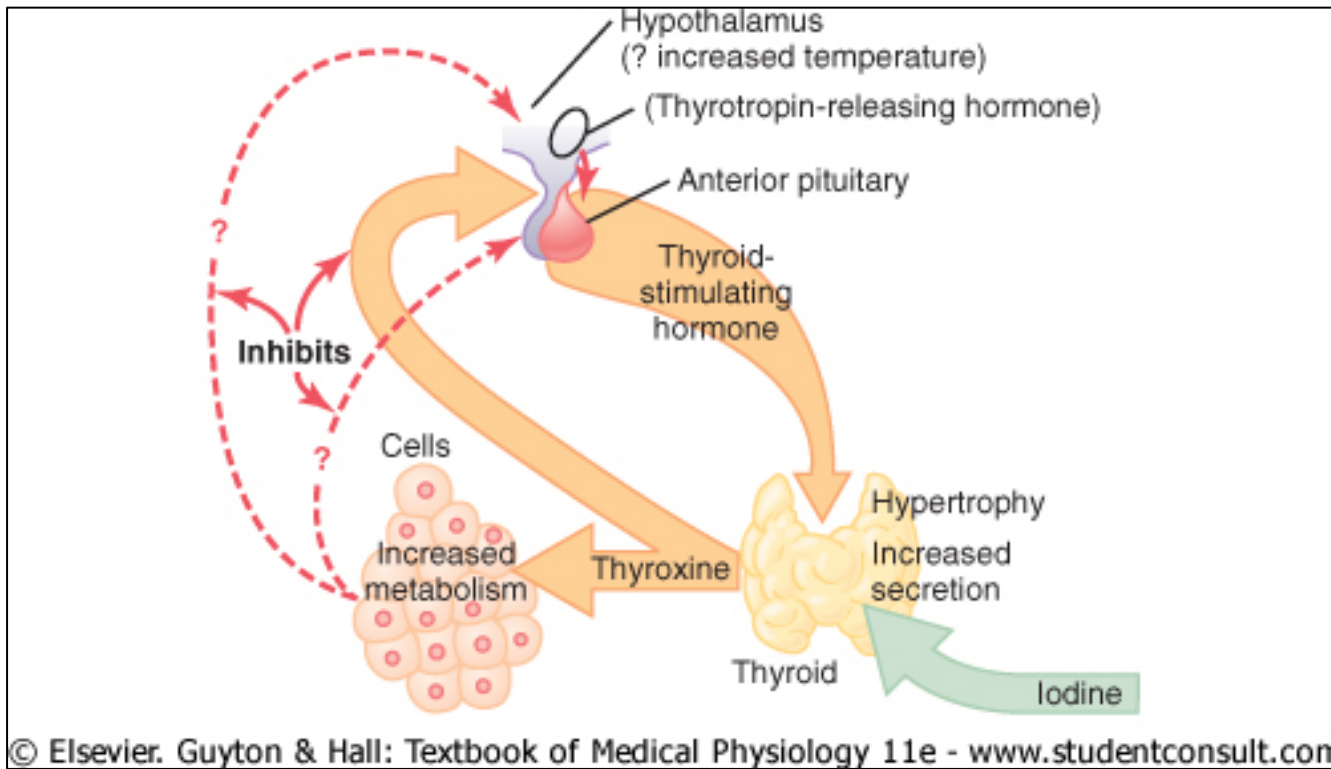
# Thyroid Axis





# TRH

- Tripeptide; regulates TSH secretion and synthesis
- The TRH receptor is G-protein coupled
  - Activation of phospholipase C
  - Hydrolysis of PIP<sub>2</sub> to IP<sub>3</sub> and diacylglycerol
  - IP<sub>3</sub> stimulates release of intracellular Ca<sup>++</sup>
  - Ca<sup>++</sup> stimulates TSH release
  - Diacylglycerol simultaneously activates PKC
  - PKC stimulates TSH  $\alpha$  and  $\beta$  subunit gene transcription
  - TRH also regulates TSH glycosylation
- TRH  $\uparrow$  by a decrease in serum T<sub>3</sub> or T<sub>4</sub>
- TRH  $\downarrow$  by an increase in serum T<sub>3</sub> or T<sub>4</sub>

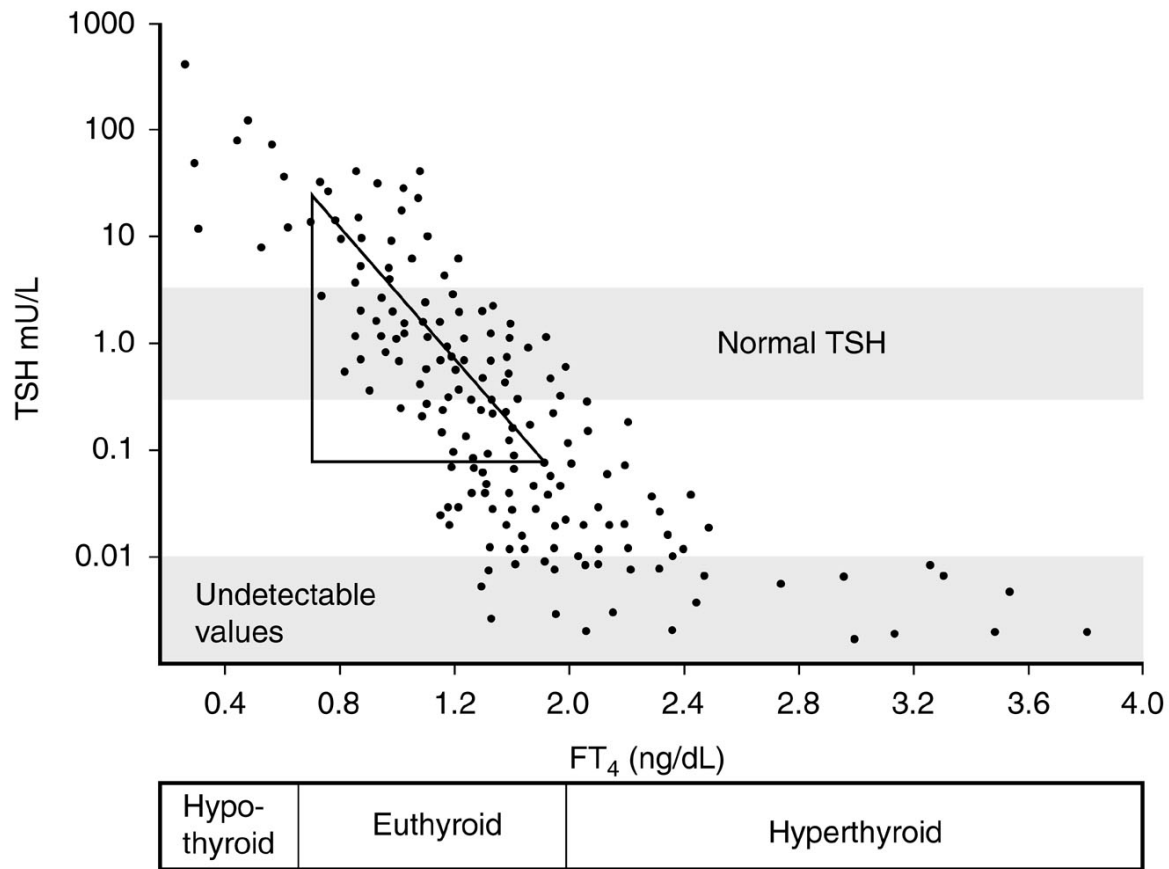


## Regulation of thyroid secretion.

# Thyroid Hormone Regulation

- Four mechanisms
  - 1. Classic hypothalamic-pituitary-thyroid axis
  - 2. Pituitary and peripheral deiodinases
  - 3. Thyroid autoregulation, response to iodine
  - 4. TSH receptor antibodies

# Log-Linear Relationship of TSH and T4



# Euthyroid Sick Syndrome

- Occurs in acute and chronic illness.
- Derangements of thyroid hormone levels are due to alterations in peripheral metabolism of  $T_4$  and binding of  $T_4$  to TBG. Fasting or illness also decrease the magnitude of TSH pulsations.
- Low  $T_4$  belays poor prognosis.

# Euthyroid Sick Syndrome

Severity of Illness	Free T4	Free T3	Reverse T3	TSH
Mild	Normal	Reduced up to 50%	Increased up to twofold	Normal
Moderate	Increased	Reduced up to 90%	Increased up to several fold	Normal
Severe	Reduced	Almost undetectable	Variable	Reduced

# The End

- Questions?

