

Thyroid Metabolic Hormones

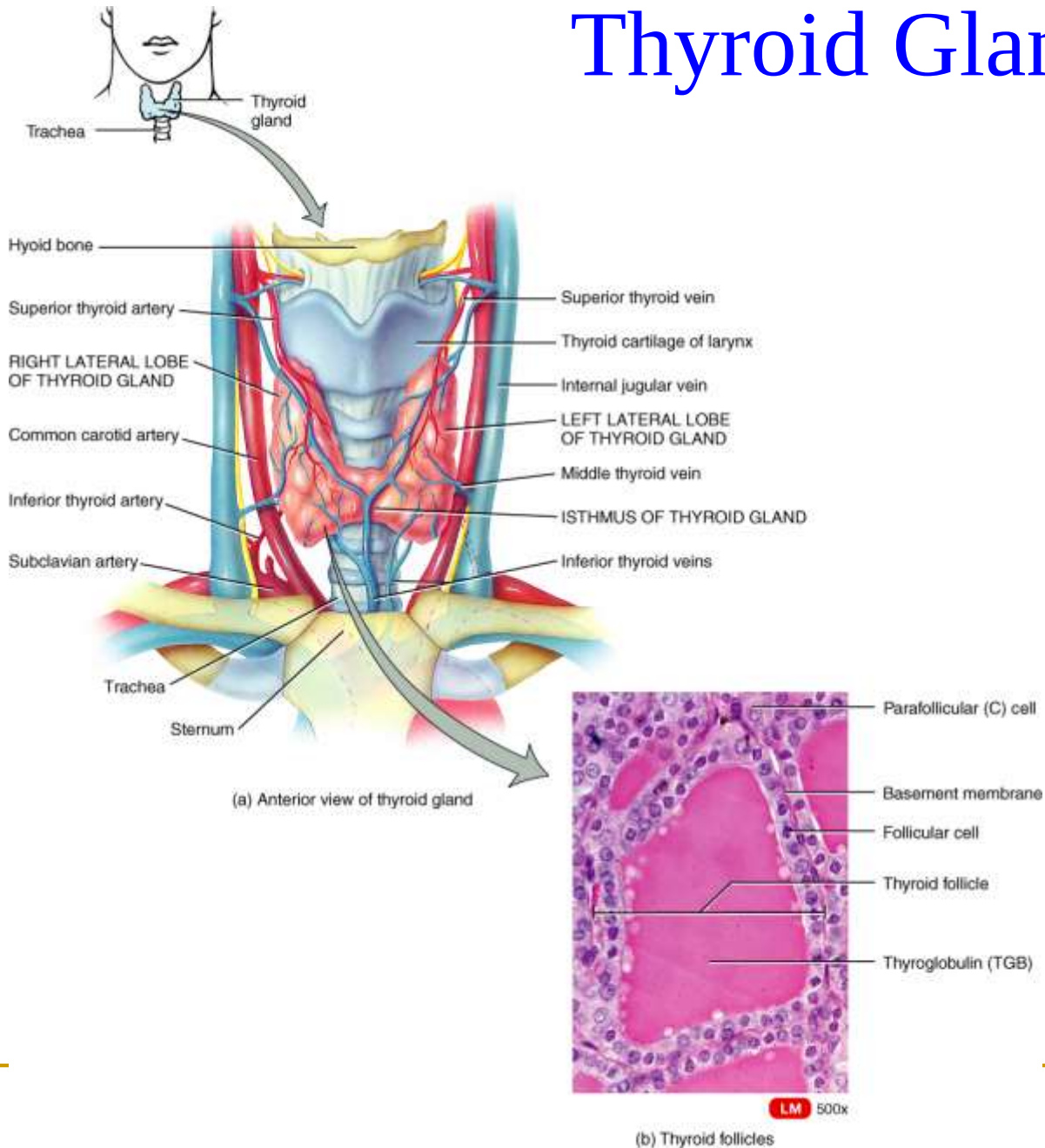
Objectives

- Illustrate thyroid hormone synthesis, storage and secretions
- Describe factors that control the synthesis, storage, and release of thyroid hormones.
- Explain the actions of thyroid hormones on development and metabolism.
- Review the mechanism of thyroid hormone actions
- Understand the causes and consequences of over-secretion and under-secretion of thyroid hormones.
Explain why either condition can cause an enlargement of the thyroid gland.

Thyroid Gland

- Located inferior to larynx
- 2 lobes connected by isthmus
- Thyroid follicles produce thyroid hormones
 - Thyroxine or tetraiodothyronine (T_4)
 - Triiodothyronine (T_3)
 - Both increase BMR, stimulate protein synthesis, increase use of glucose and fatty acids for ATP production
- Parafollicular cells or C cells produce calcitonin
 - Lowers blood Ca^{2+} by inhibiting bone resorption

Thyroid Gland



Production of Thyroid Hormones

- Iodide (I^-) actively transported into the follicle and secreted into the colloid.
- Oxidized to iodine (I^0).
- Iodine attached to tyrosine within thyroglobulin chain.
 - Attachment of 1 iodine produces monoiodotyrosine (MIT).
 - Attachment of 2 iodines produces diiodotyrosine (DIT).
- MIT and DIT or 2 DIT molecules coupled together.

Production of Thyroid Hormones (continued)

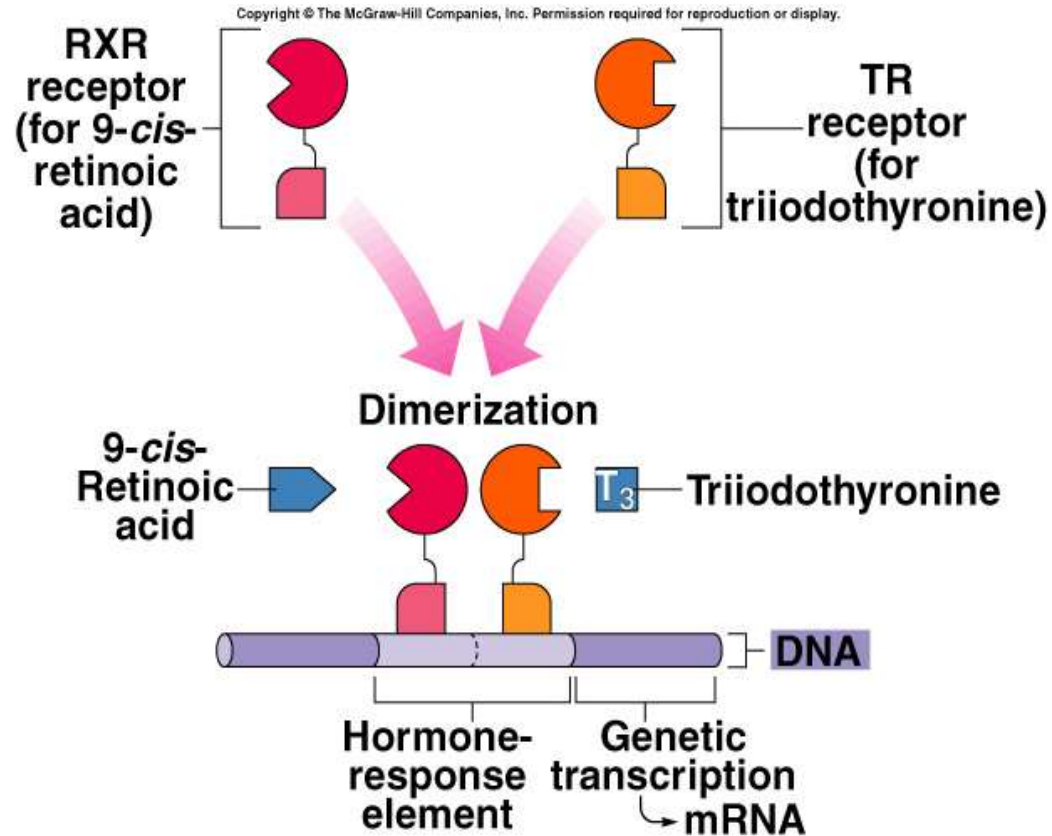
- T_3 and T_4 produced.
- TSH stimulates pinocytosis into the follicular cell.
 - Enzymes hydrolyze T_3 and T_4 from thyroglobulin.
- Attached to TBG and released into blood.

Control of thyroid hormone secretion

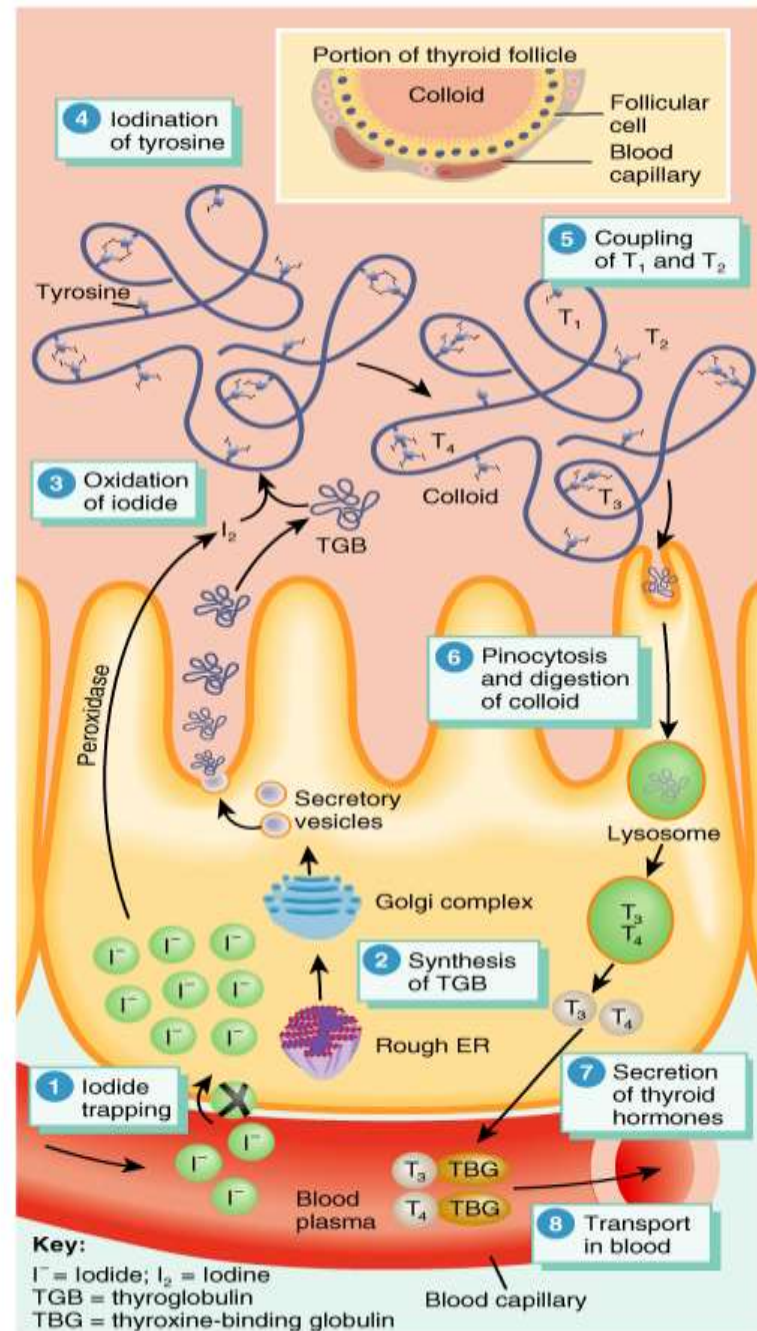
- ❑ Thyrotropin-releasing hormone (TRH) from hypothalamus
- ❑ Thyroid-stimulating hormone (TSH) from anterior pituitary
- ❑ Situations that increase ATP demand also increase secretion of thyroid hormones

Mechanism of Thyroid Hormone Action

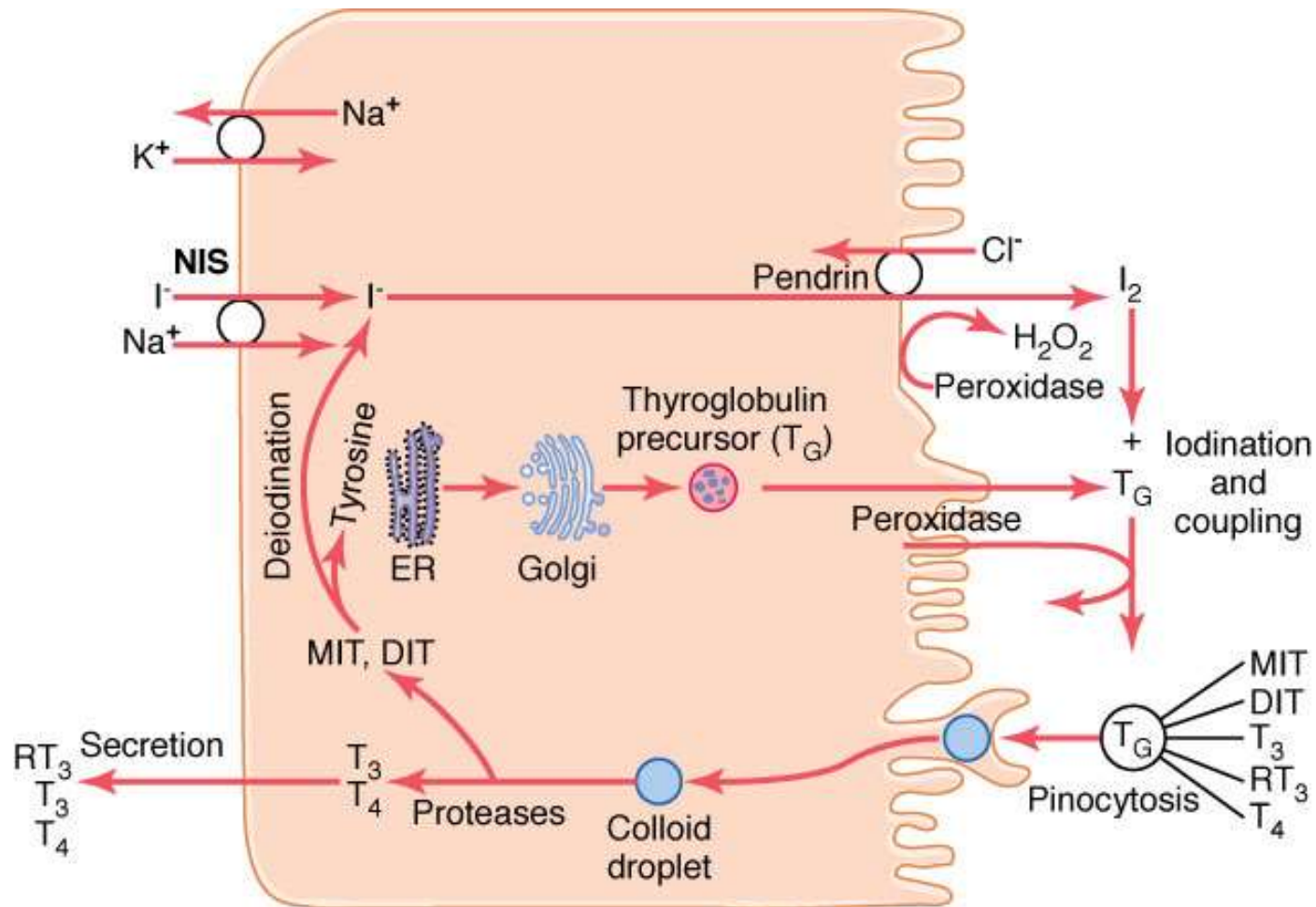
- T_4 passes into cytoplasm and is converted to T_3 .
- Receptor proteins located in nucleus.
 - T_3 binds to ligand-binding domain.
 - Other half-site is vitamin A derivative (9-cis-retinoic) acid.
 - DNA-binding domain can then bind to the half-site of the HRE.
 - Two partners can bind to the DNA to activate HRE.
 - Stimulate transcription of genes.



Synthesis of thyroid hormones



Thyroid Hormone Synthesis & Secretion



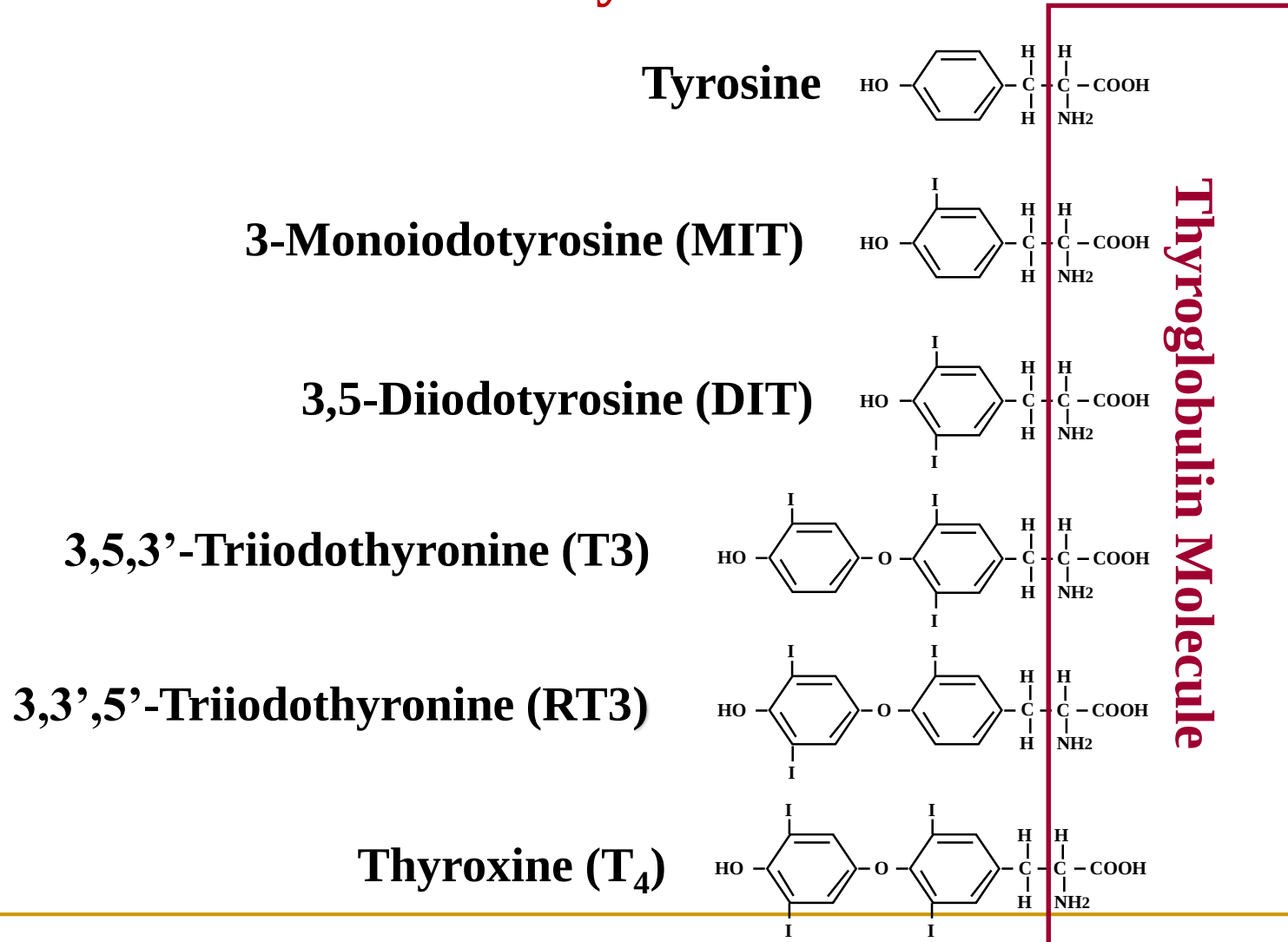
Thyroid Hormones

- T_3 (triiodothyronine)
- T_4 (thyroxine)

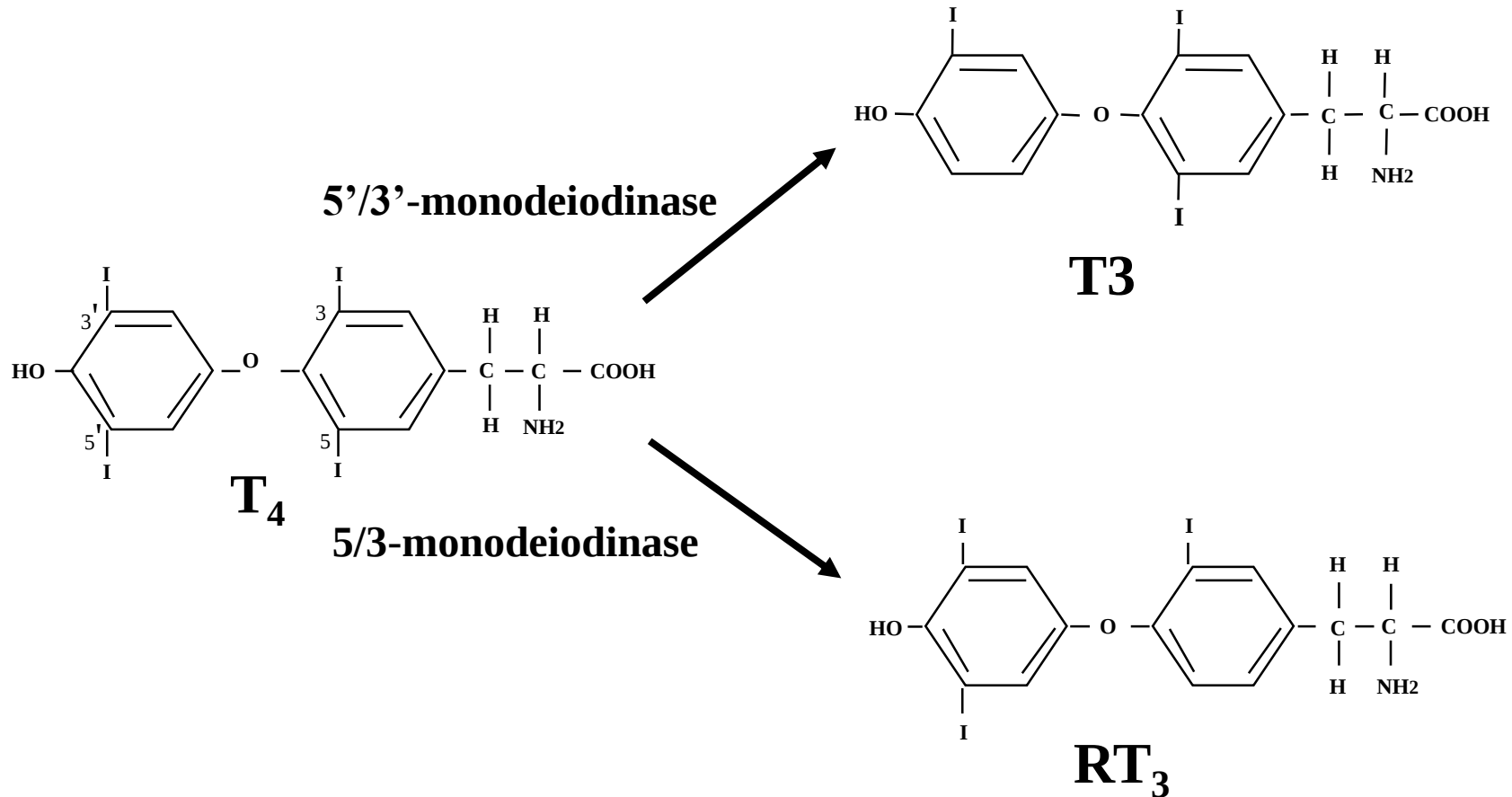
Thyroid Hormone Synthesis & Secretion

EVENT	SITE	ENZYME	INHIBITOR
1 Synthesis of TG; extrusion into follicular lumen	Rough ER, Golgi apparatus		
2 I ⁻ pump	Basal membrane		Perchlorate, thiocyanate
3 Oxidation of I ⁻ → I ₂ membrane	Apical (luminal)	Peroxidase	Propylthiouracil (PTU)
4 Organification of I ₂ into MIT & DIT	Apical Membrane	Peroxidase	Propylthiouracil
5 Coupling reaction of MIT & DIT into T ₃ & T ₄	Apical Membrane	Peroxidase	Propylthiouracil
6 Endocytosis of TG	Apical Membrane		
7 Hydrolysis of T ₄ , T ₃ , RT ₃ , MIT, DIT; T ₄ , T ₃ , & RT ₃ enter circulation	Lysosomes	Proteases	
8 Deiodination of residual MIT & DIT. Recycling of I ⁻ & Tyrosine	Intracellular	Deiodinase	

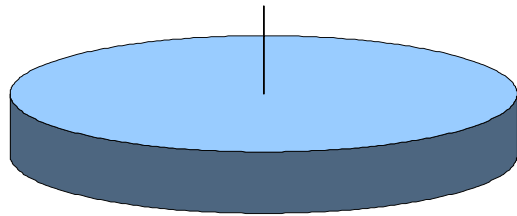
Binding of THs & Precursors to TG During Hormone Synthesis



Metabolism of Thyroxine by Deiodination in Peripheral Tissues



Thyroid Hormone Production



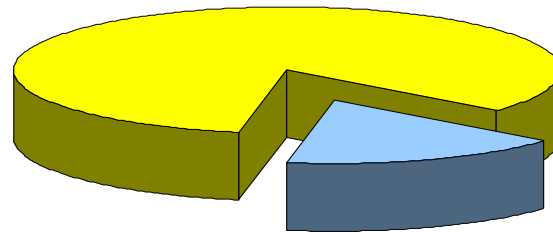
T₄
80 ug/day



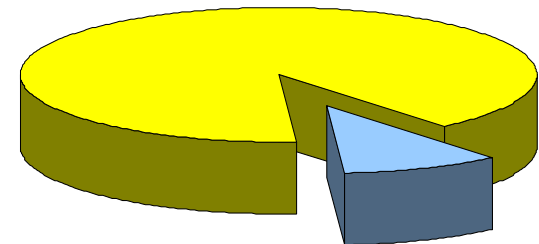
Secreted by thyroid



**Deiodination of T₄ in
peripheral tissues**



T₃
31 ug/day



RT₃
38 ug/day

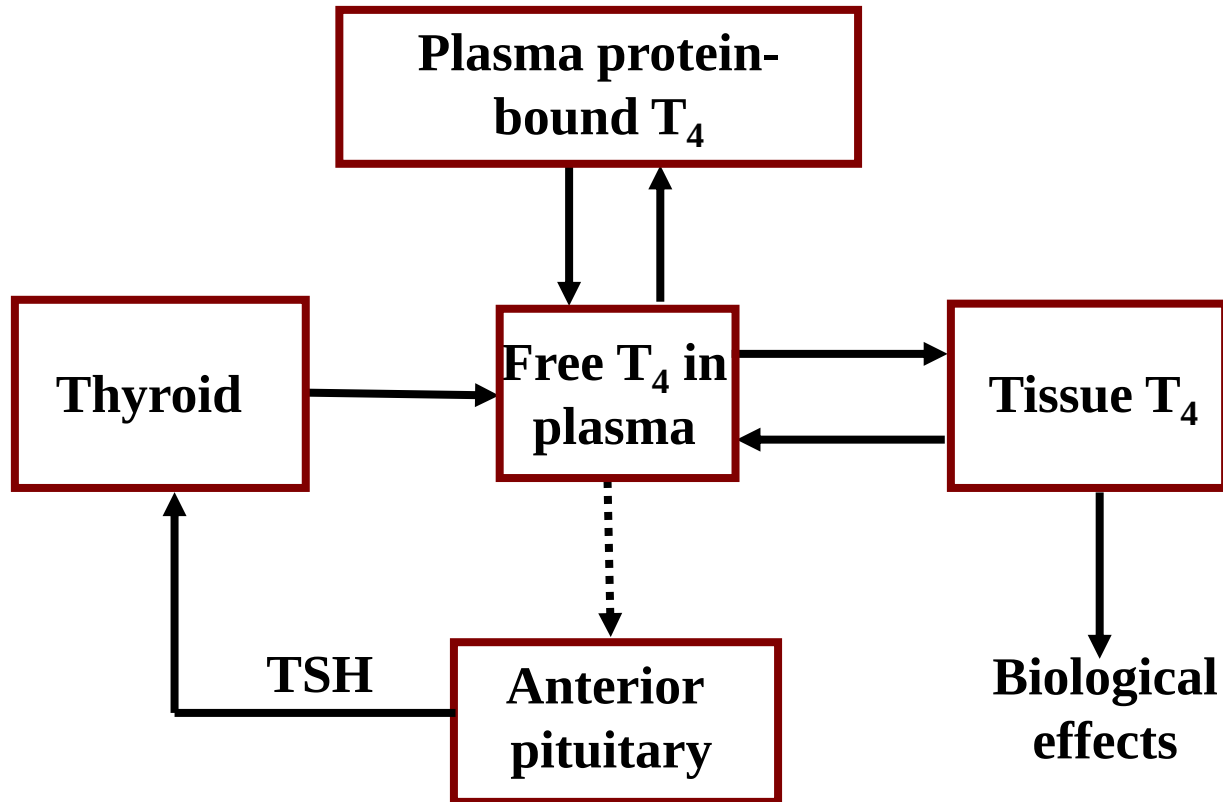
Circulating Transport Proteins

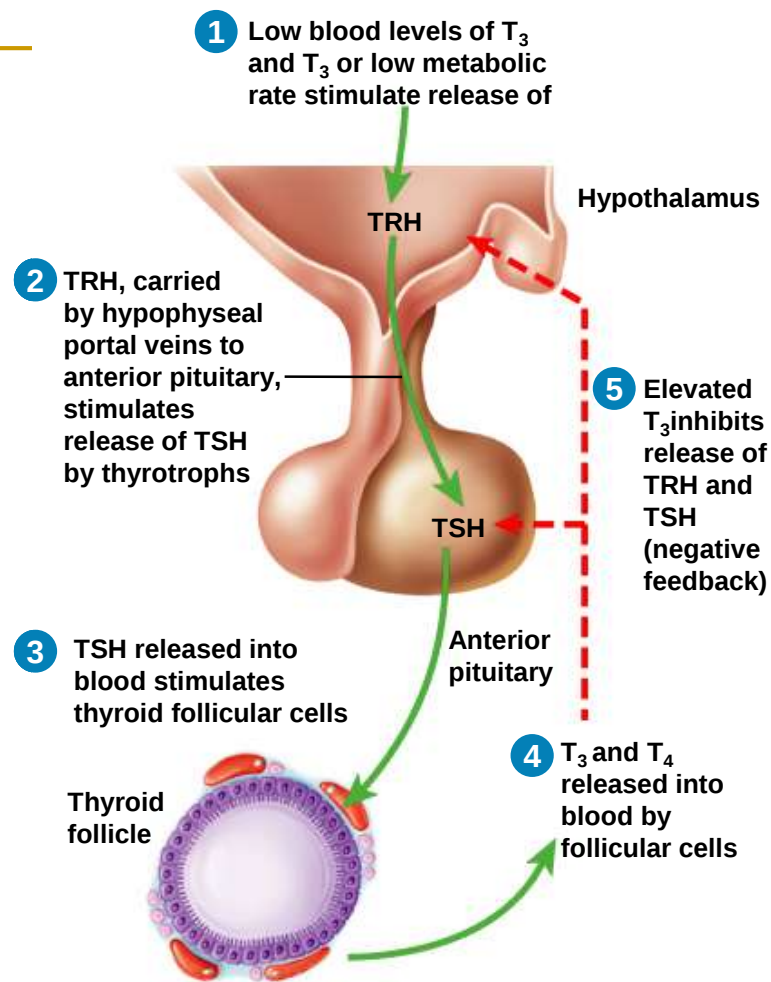
Transport Protein	Principle Hormone Transported
Specific	
Corticosteroid binding globulin (CBG, transcortin)	Cortisol, aldosterone
Thyroxine binding globulin (TBG)	Thyroxine, triiodothyronine
Sex hormone-binding globulin (SHBG)	Testosterone, estrogen
Nonspecific	
Albumin	Most steroids, thyroxine, triiodothyronine
Transthyretin (prealbumin)	Thyroxine , some steroids

Steady-State Effects of Variations in Plasma [TH-Binding Proteins]

Condition	Concentrations of Binding Proteins	Total Plasma T_4, T_3, RT_3	Free Plasma T_4, T_3, RT_3	Plasma TSH	Clinical State
Hyperthyroidism	Normal	High	High	Low	Hyperthyroid
Hypothyroidism	Normal	Low	Low	High	Hypothyroid
Estrogens, pregnancy	High	High	Normal	Normal	Euthyroid
Liver disease, glucocorticoids, androgens	Low	Low	Normal	Normal	Euthyroid

Interrelationships Between Free & Bound T₄

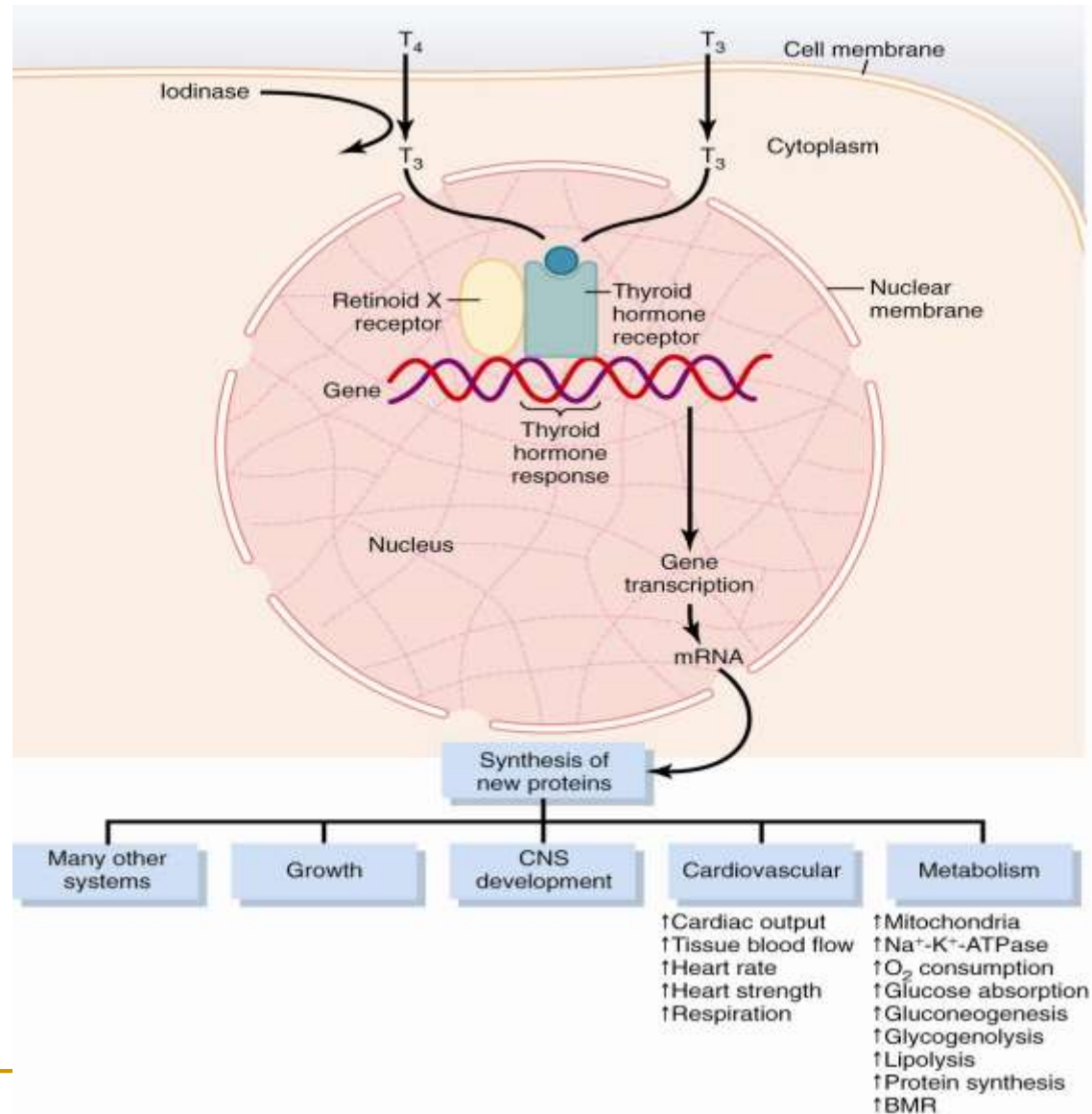




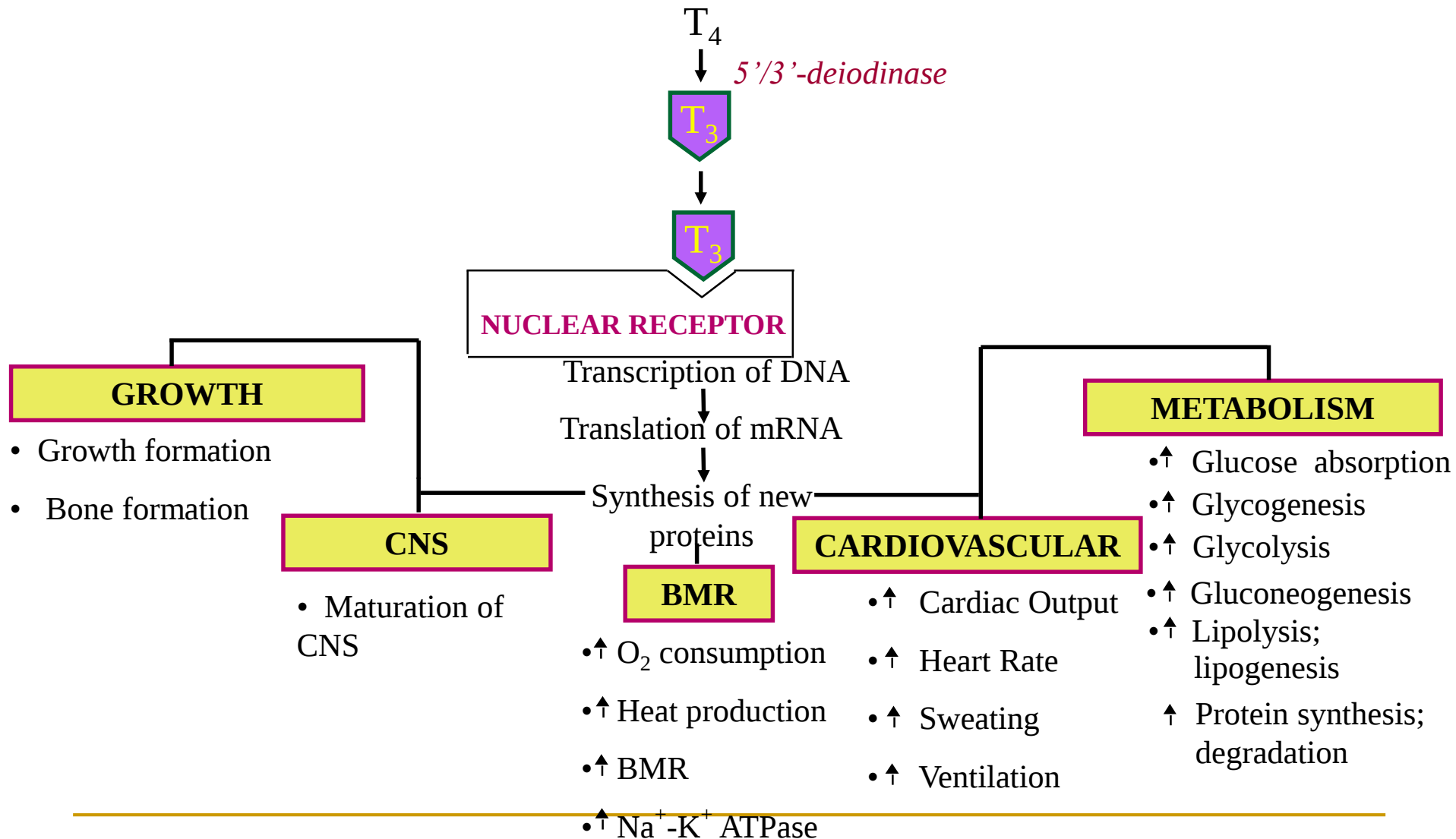
Actions of Thyroid Hormones:

- Increase basal metabolic rate
- Stimulate synthesis of Na^+/K^+ ATPase
- Increase body temperature (calorigenic effect)
- Stimulate protein synthesis
- Increase the use of glucose and fatty acids for ATP production
- Stimulate lipolysis
- Enhance some actions of catecholamines
- Regulate development and growth of nervous tissue and bones

Actions of Thyroid Hormones



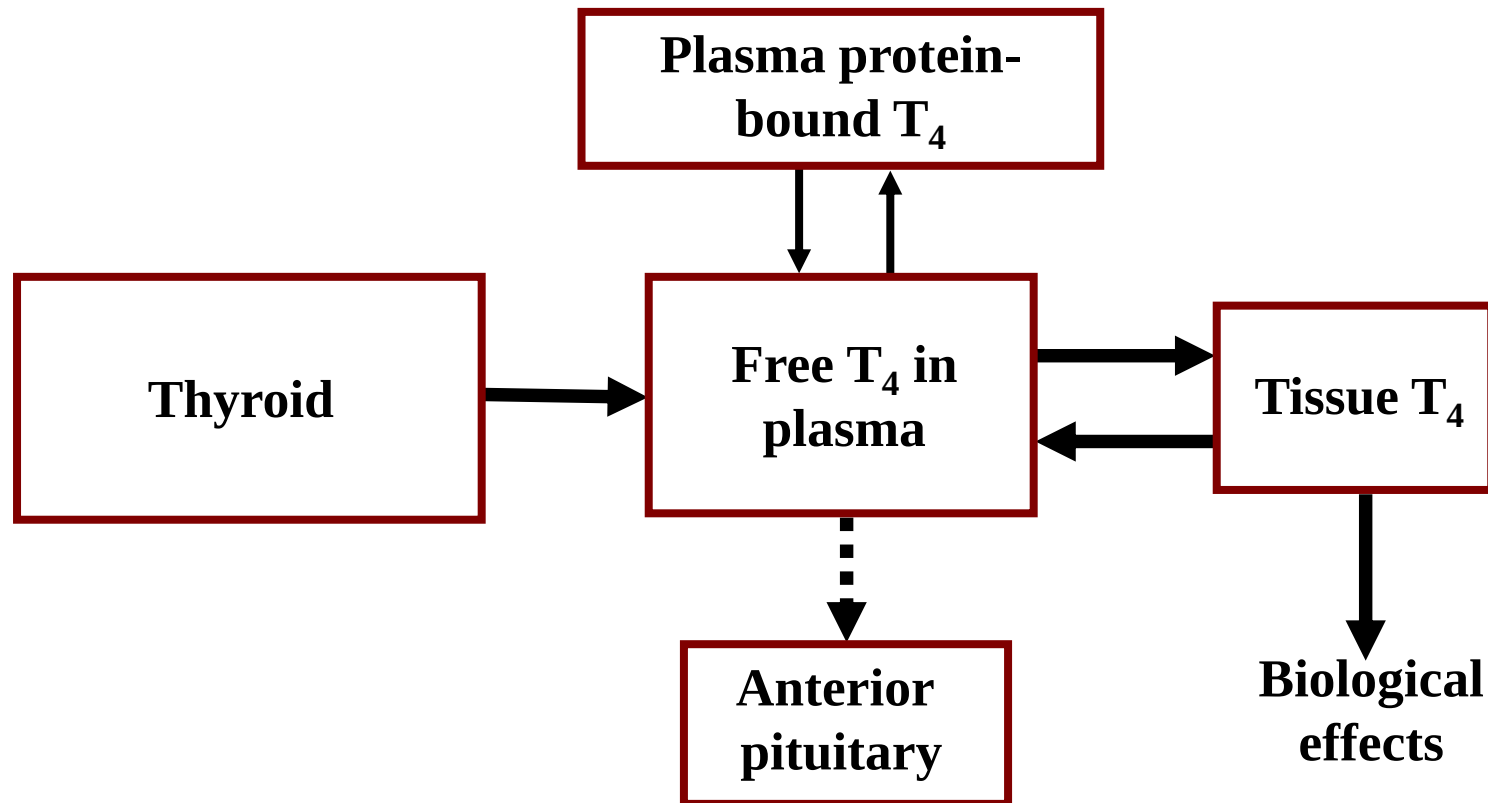
Actions of Thyroid Hormones



Actions of T_3

- Stimulates protein synthesis.
- Promotes maturation of nervous system.
- Stimulates rate of cellular respiration by:
 - Production of uncoupling proteins.
 - Increase active transport by Na^+/K^+ pumps.
 - Lower cellular [ATP].
- Increases metabolic heat.
- Increases metabolic rate.
 - Stimulates increased consumption of glucose, fatty acids and other molecules.

Interrelationships Between Free & Bound T_4 --Increased T_4 Secretion



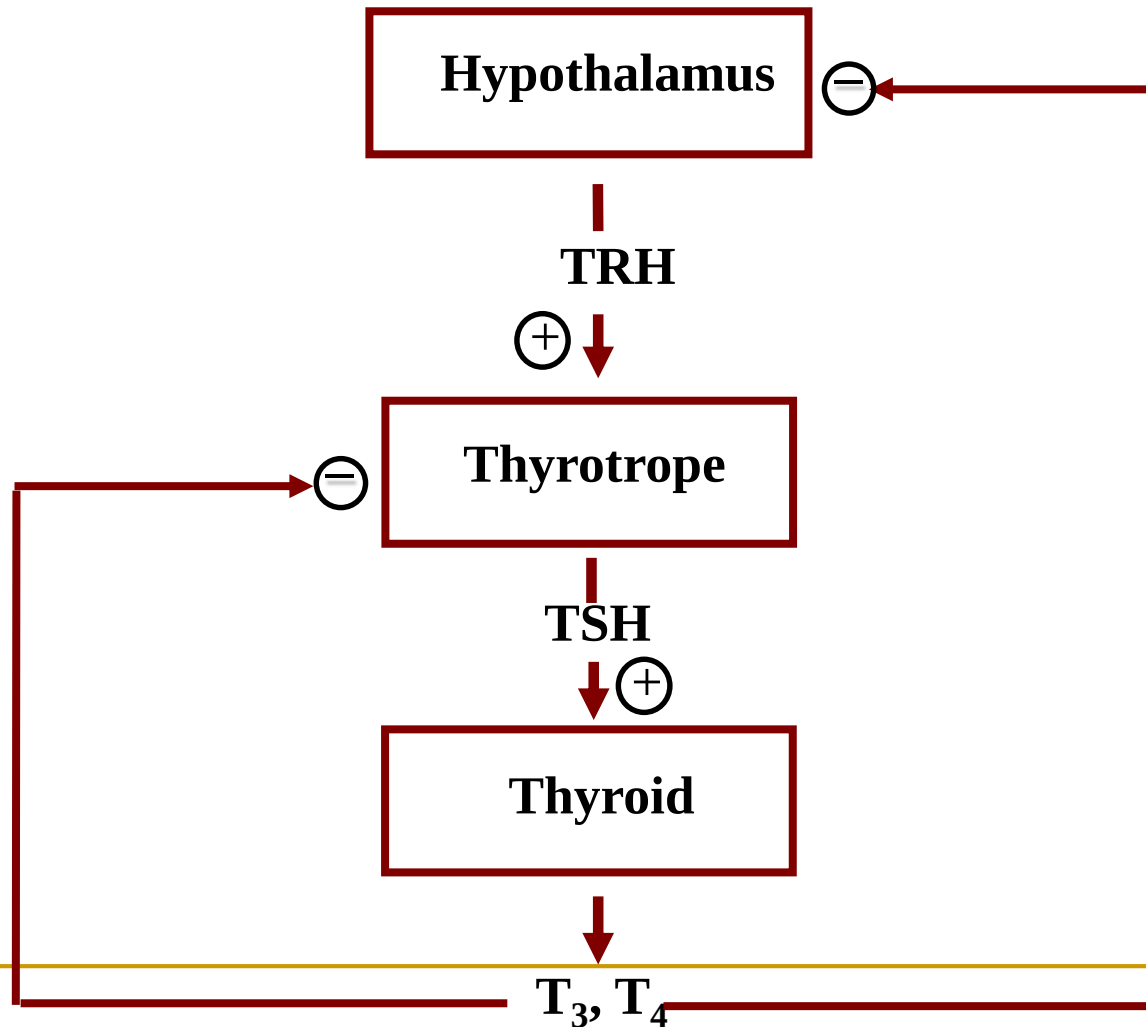
Steady-State Effects of Variations in Plasma [TH-Binding Proteins]

Condition	Concentrations of Binding Proteins	Total Plasma T_4, T_3, RT_3	Free Plasma T_4, T_3, RT_3	Plasma TSH	Clinical State
Hyperthyroidism	Normal	High	High	Low	Hyperthyroid
Hypothyroidism	Normal	Low	Low	High	Hypothyroid
Estrogens, pregnancy	High	High	Normal	Normal	Euthyroid
Liver disease, glucocorticoids, androgens	Low	Low	Normal	Normal	Euthyroid

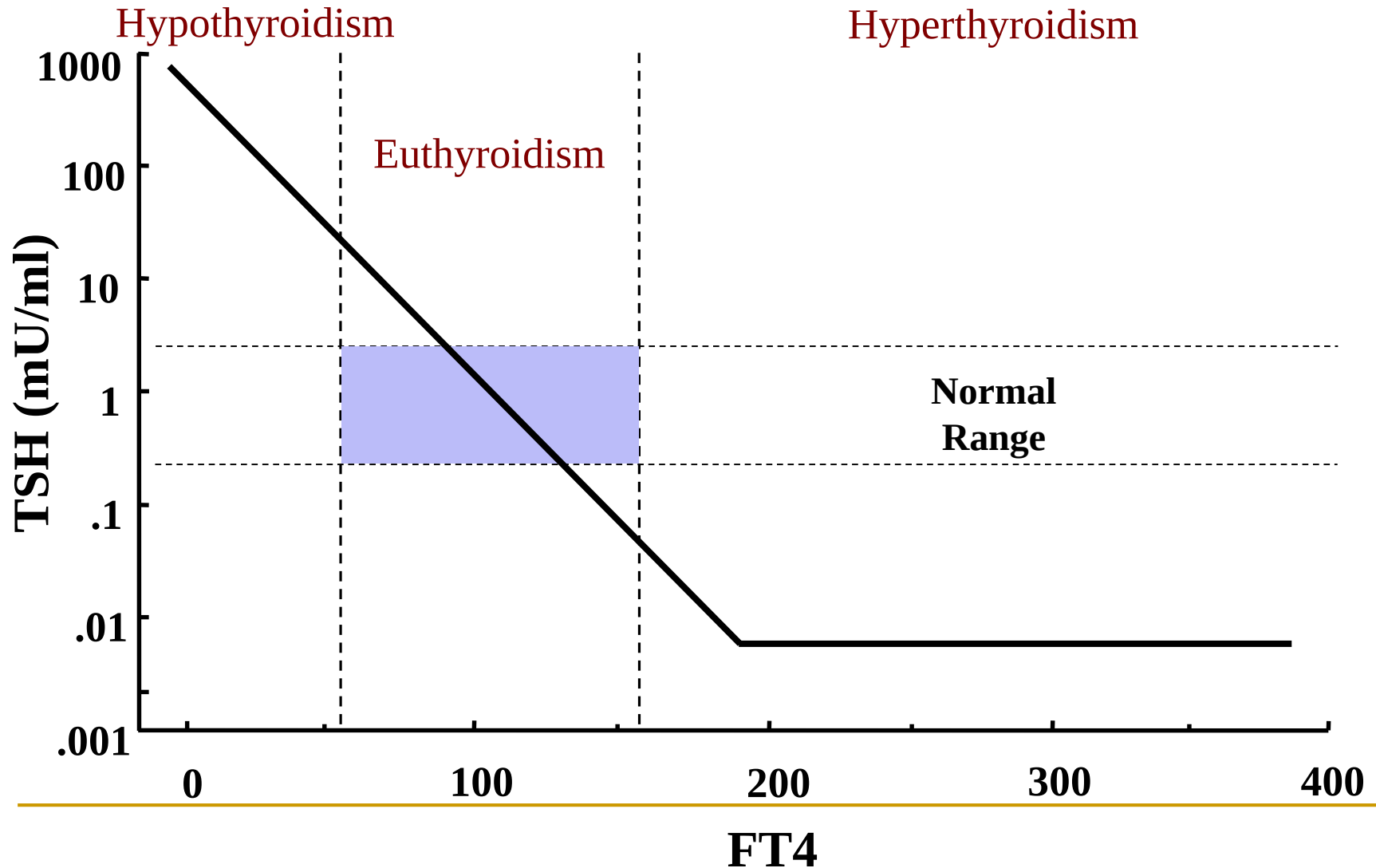
Metabolic Effects of Thyroid Hormones

Parameter	↓ T ₃ , T ₄	↑ T ₃ , T ₄
Basal metabolic rate	↓	↑
Carbohydrate metabolism	↓ Gluconeogenesis ↓ Glycogenolysis	↑ Gluconeogenesis ↑ Glycogenolysis ↑ Glycolysis
	Normal serum [glucose]	Normal serum [glucose]
Protein metabolism	↓ Synthesis ↓ Proteolysis	↑ Synthesis ↑ Proteolysis Muscle wasting
Lipid metabolism	↓ Lipogenesis ↓ Lipolysis ↑ Serum [cholesterol]	↑ Lipogenesis ↑ Lipolysis ↓ Serum [cholesterol]
Thermogenesis	↓	↑

Hypothalamohypophyseal-Thyroid Axis

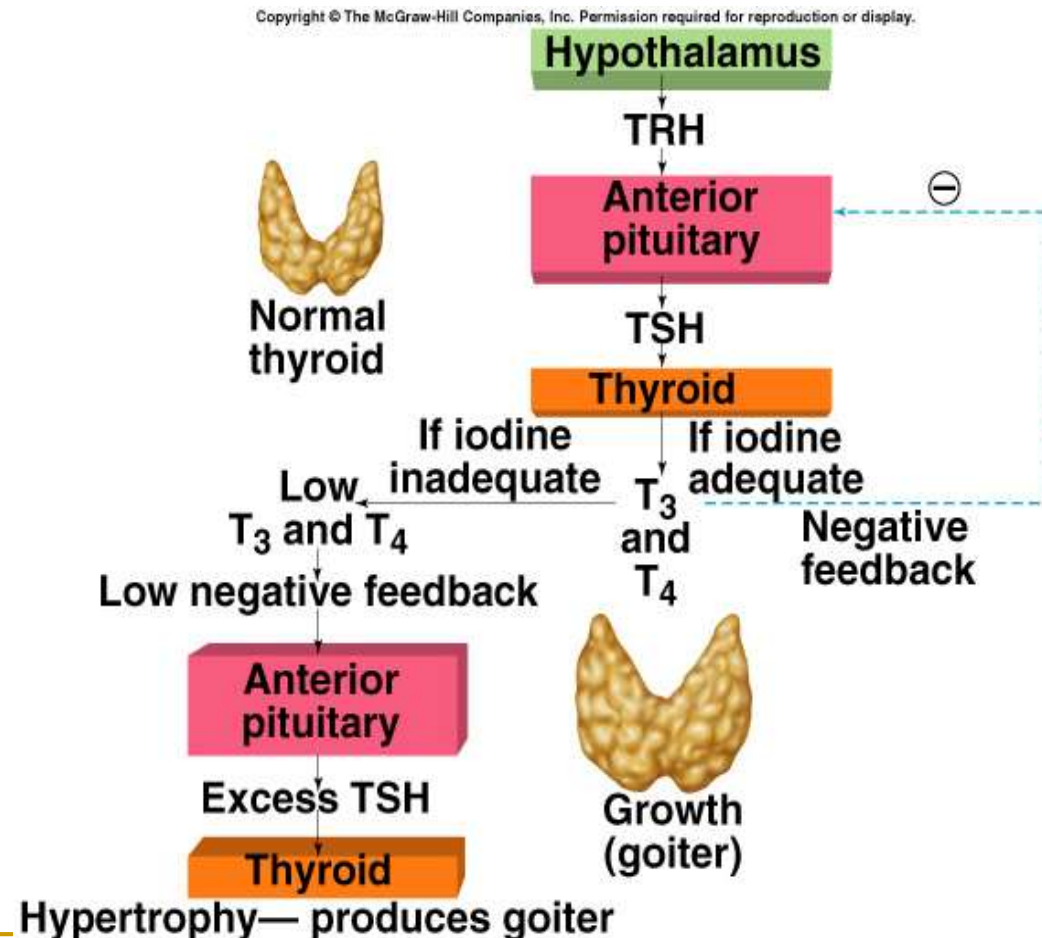


Relationship Between Plasma TSH & Free T4



Diseases of the Thyroid

- Iodine-deficiency (endemic) goiter:
 - Abnormal growth of the thyroid gland.
 - In the absence of sufficient iodine, cannot produce adequate amounts of T_4 and T_3 .
 - Lack of negative feedback inhibition.
 - Stimulates TSH, which causes abnormal growth.



Causes of Thyrotoxicosis

■ **Primary hyperthyroidism**

- ❑ Graves' disease (most common form of thyrotoxicosis)
- ❑ Toxic multinodular goiter
- ❑ Toxic adenoma
- ❑ Thyroid carcinoma

■ **Thyrotoxicosis without hyperthyroidism**

- ❑ Thyroiditis
- ❑ Iatrogenic

■ **Secondary hyperthyroidism**

- ❑ TSH-secreting pituitary adenoma
- ❑ Hypothalamic disease

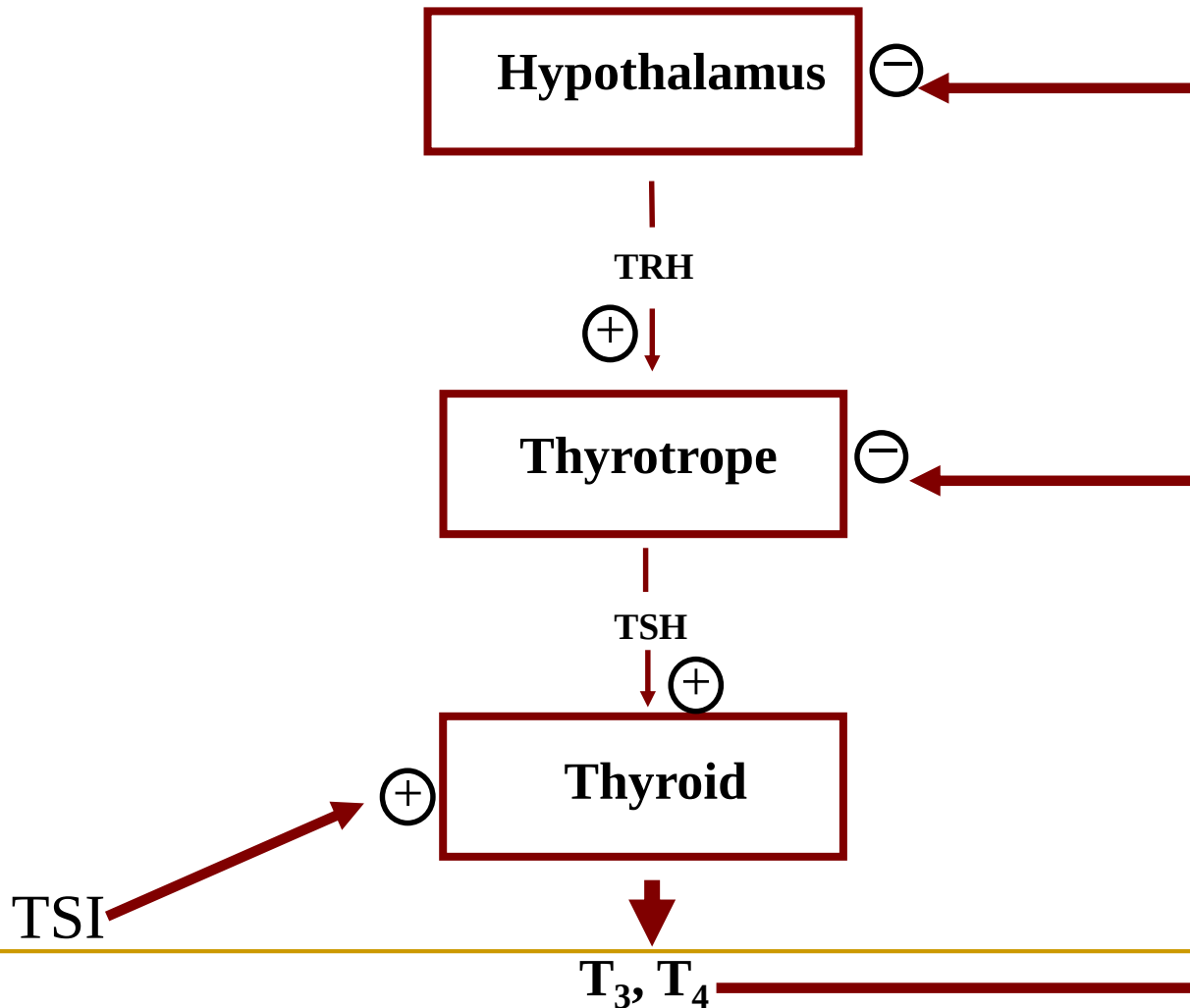
Prevalent Endocrine Disorders in the Adult

<u>Disorder</u>	<u>Prevalence</u>
• Type II DM	~8%
• Hypothyroidism	5-10%, ♀ 0.5-2%, ♂
• Graves' disease	1-3%, ♀ .1%, ♂
• Thyroid nodules	5%
• Osteoporosis	5%, ♀ 1%, ♂
• Hyperparathyroidism	0.1-0.5%, ♀ > ♂
•	

Pathophysiology of Thyroid Hormones

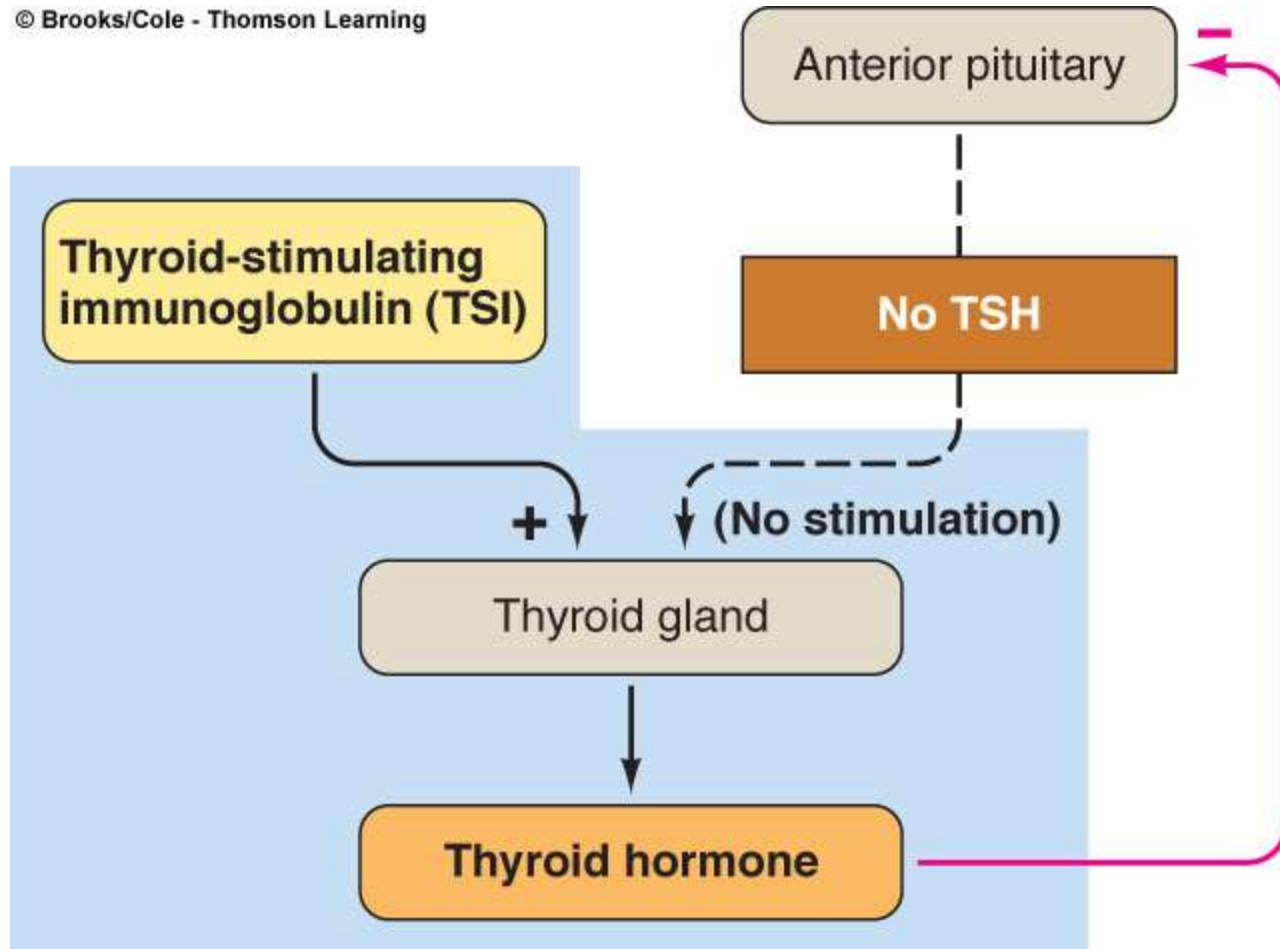
- **Graves' disease**
- Myxedema
- Cretinism

Hypothalamohypophyseal-Thyroid Axis in Graves' Disease



Role of Thyroid-Stimulating Immunoglobulin in Graves' Disease

© Brooks/Cole - Thomson Learning



Signs & Symptoms of Thyrotoxicosis

Descending Order of Frequency

Symptoms

Hyperactivity, irritability, dysphoria
(dissatisfaction)
Heat intolerance & sweating
Palpitations
Fatigue & weakness
Weight loss & increased appetite
Diarrhea
Oligomenorrhea

Signs

Tachycardia, atrial fibrillation

Tremor
Goiter

Warm moist skin
Muscle weakness, proximal myopathy

Lid retraction or lag
Gynecomastia

Signs & Symptoms of Hypothyroidism

Descending Order of Frequency

Symptoms

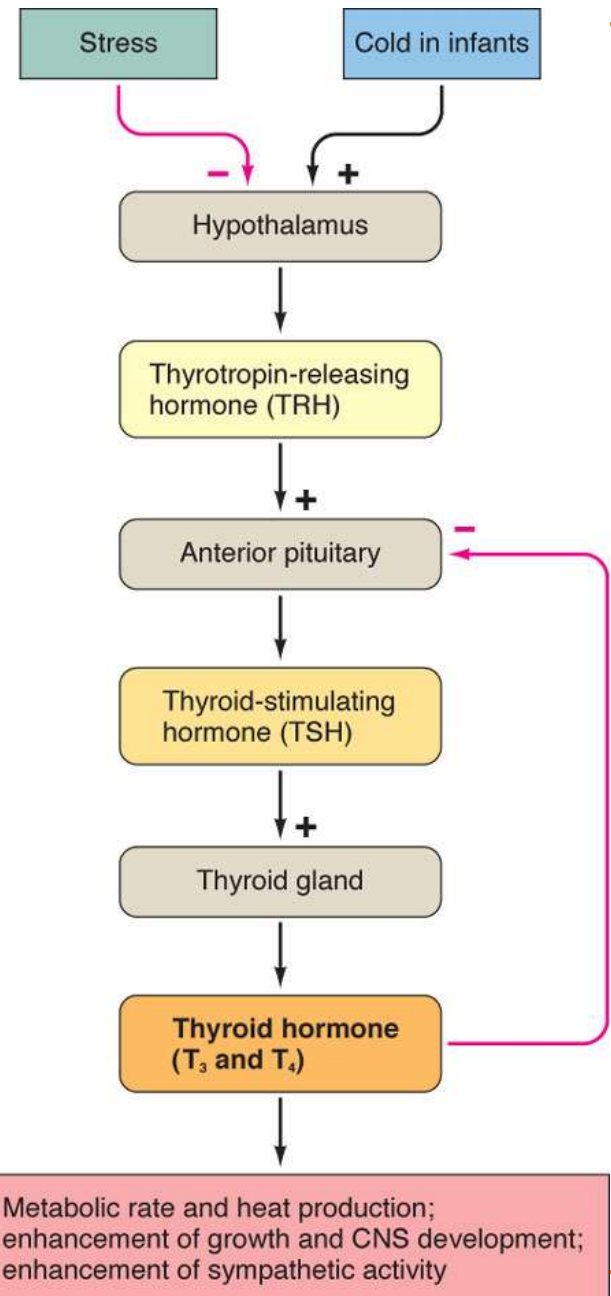
Weakness, tiredness
Dry skin
Feeling cold
Hair loss
Difficulty concentrating & poor memory
Constipation
Weight gain & poor appetite
Dyspnea
Hoarse voice
Menorrhagia
Paresthesia

Signs

Dry coarse skin, cool extremities
Puffy face, hands, & feet (myxedema)
Diffuse alopecia
Bradycardia
Peripheral edema
Delayed tendon reflex relaxation
Carpal tunnel syndrome

Sluggish: S=Sleepiness, fatigue, tiredness L=Loss of memory U=Unusually dry skin
G=Goiter G=Gradual personality change I=Increase in body weight
~~S=Sensitivity to cold H=Hair loss, sparseness of hair~~

Regulation of Thyroid Hormone Secretion



Indirect

↑ Heat production and
CO₂ in tissues
↓
↓ Peripheral vascular
resistance
↓
↓ Diastolic blood pressure
↓
Reflex ↑ adrenergic stimulation

Direct

↑ Cardiac muscle
Myosin heavy chain α/β ratio
Na⁺, K⁺-ATPase
Sarcoplasmic Ca-ATPase
 β -Adrenergic signaling
G-protein stimulatory/
inhibitory ratio
↑ Ventricular contractility and
function
↓ Peripheral vascular
resistance

↑ Cardiac rate and output

↑ Blood volume

Direct and indirect

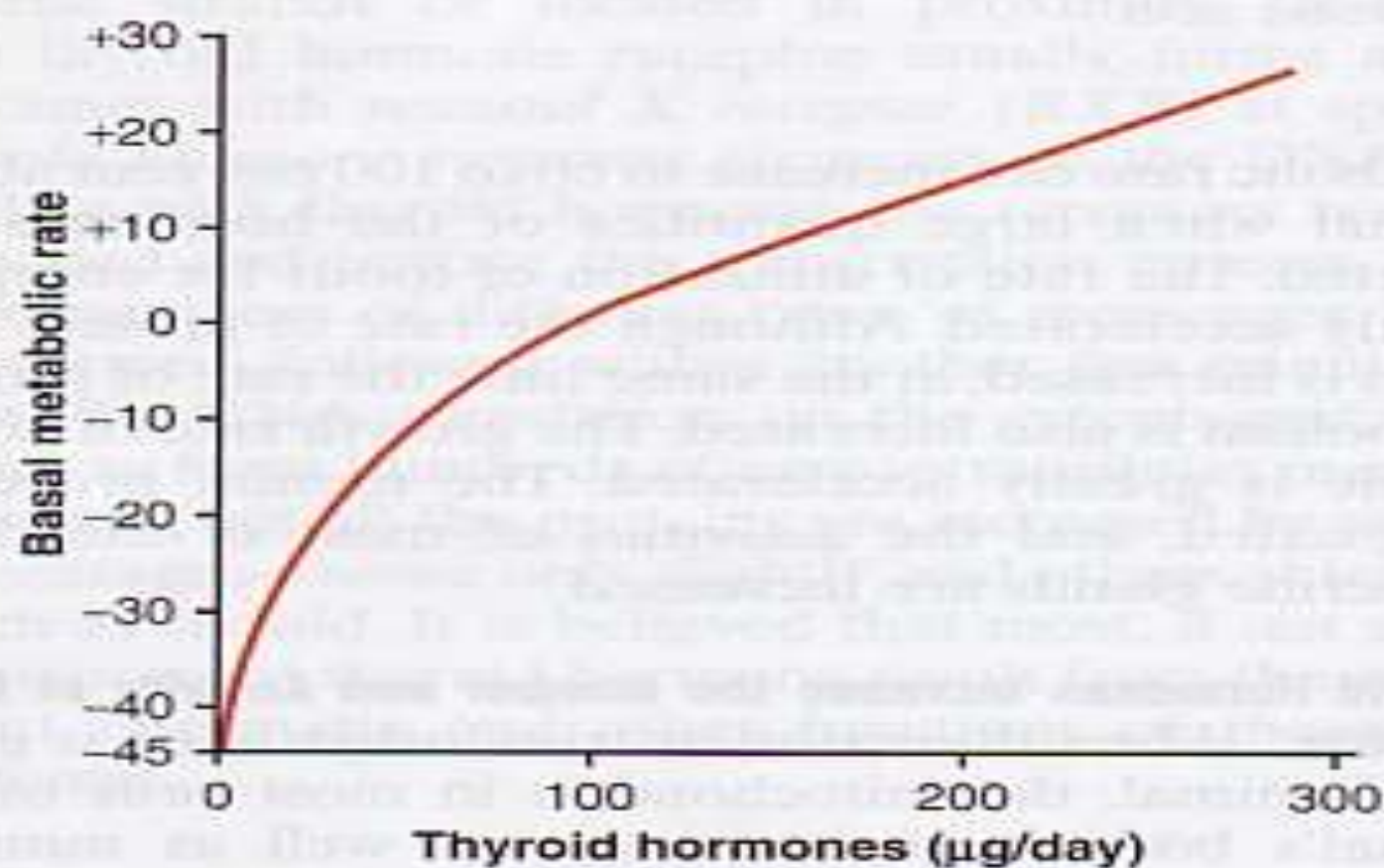


Figure 76-6

Approximate relation of daily rate of thyroid hormone (T_4 and T_3) secretion to the basal metabolic rate.

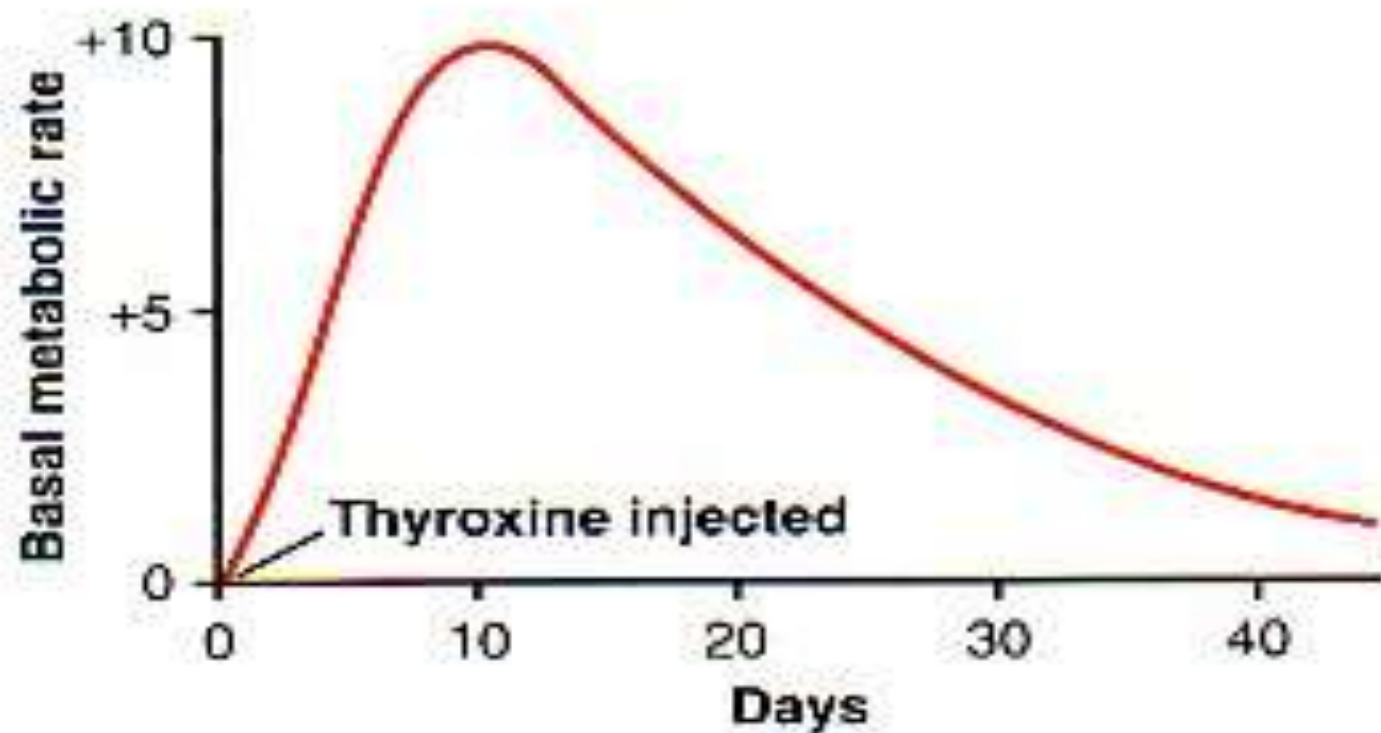


Figure 76-4

Approximate prolonged effect on the basal metabolic rate caused by administering a single large dose of thyroxine.

Thank You

