

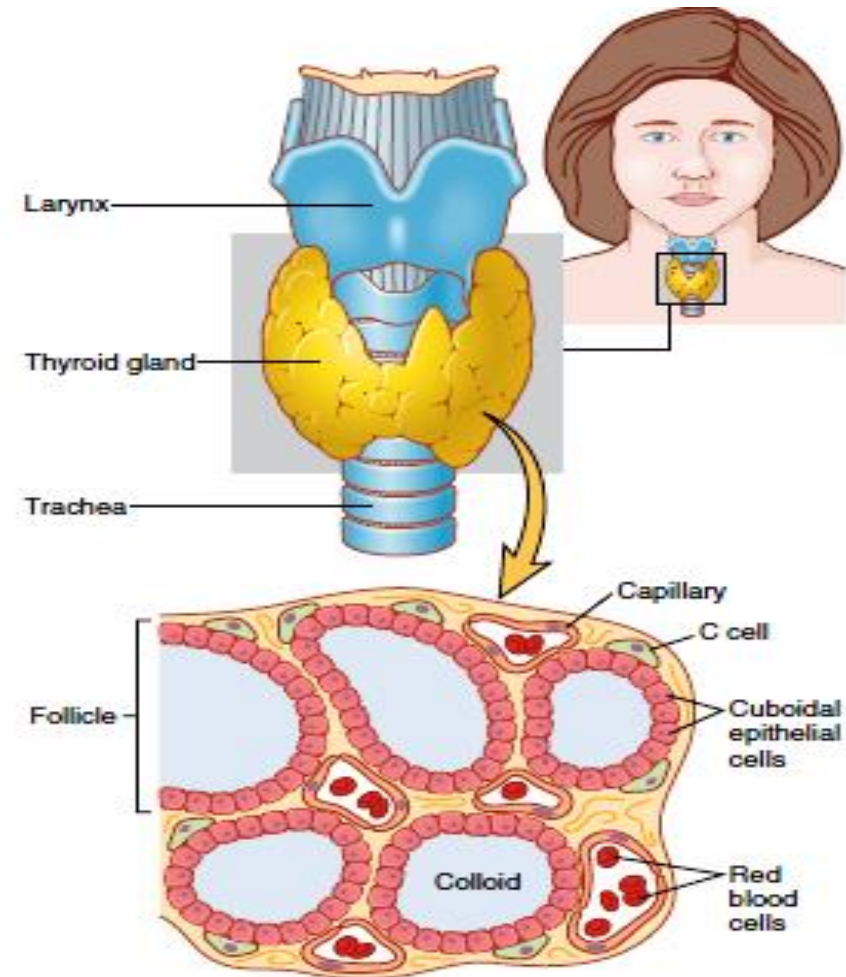
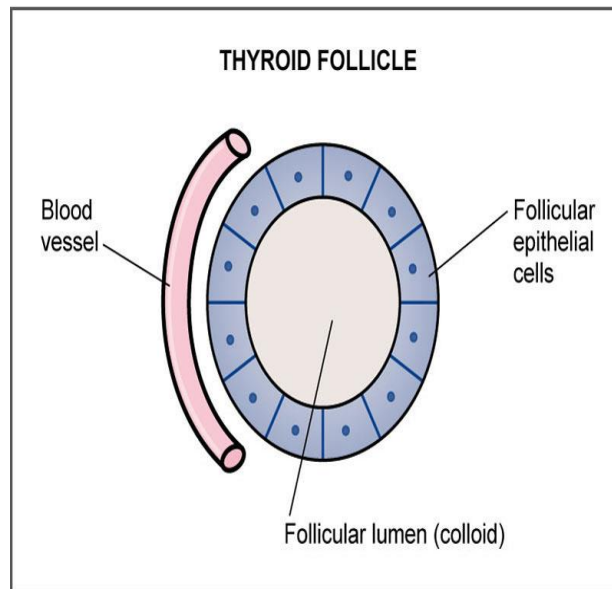
Lecture 6

Thyroid Hormones

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Thyroid gland



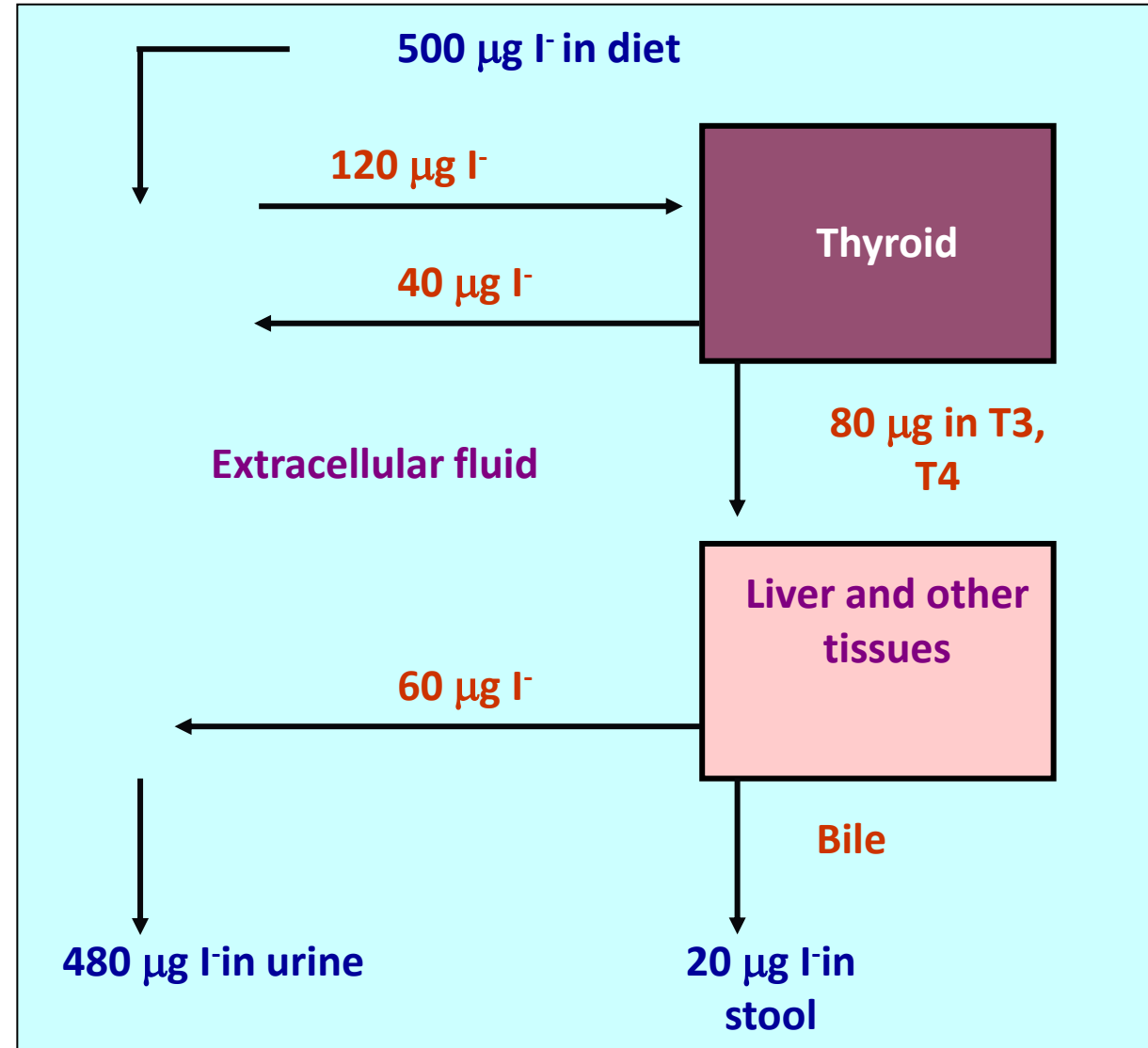
Thyroid Gland

- Involved in production, storage, and release of thyroid hormone
- Largest Endocrine organ in the body
- Complete **lack of thyroid** secretion decreases the BMR by 40%- 50%.
- Extreme **excess** of its secretion increases the **BMR** by 60%- 100%.
- Function influenced by
 - Hypothalamic Pituitary – axis
 - (**TRH**)
 - (**TSH**)
 - Environmental factors (**iodide intake**)
 - Secrets two hormones T4 , T3 by thyrocytes and calcitonin by c cells



IODINE HOMEOSTASIS

Seafood, meat, dairy products,
bread, iodinated salts



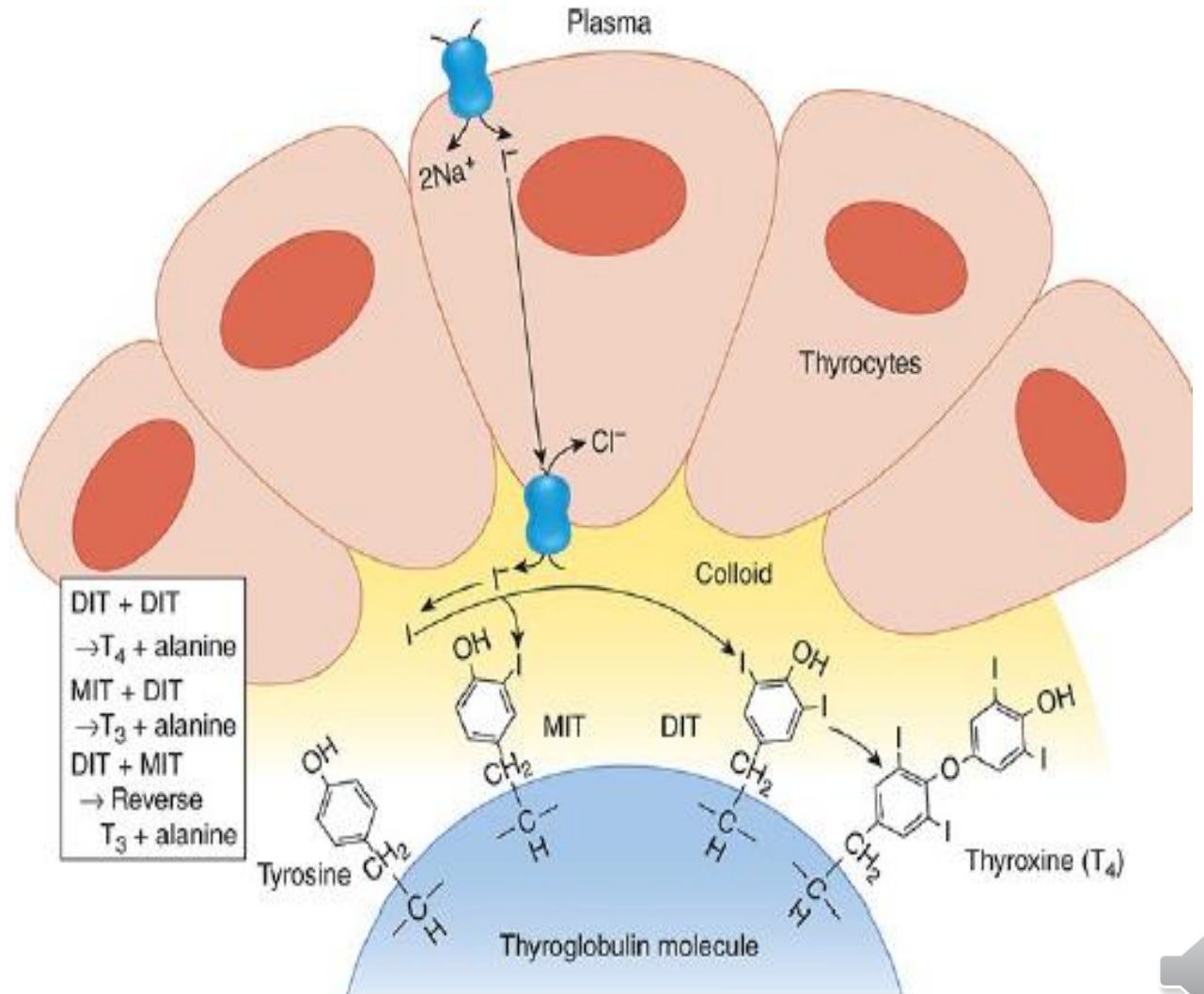
IODINE HOMEOSTASIS

- The minimum daily iodine 150 μg in adults
- about 50 milligrams of ingested iodine in the form of iodides are required *each year*, or about *1 mg/week*.
- About $1/5^{\text{th}}$ of ingested iodide is taken by the thyroid in the form of I^- , for synthesis of thyroid hormones,
- Most iodine after metabolic degradation of thyroid hormones is excreted by and the kidneys in the urine.
- About 120 $\mu\text{g}/\text{day}$ enter the thyroid at normal rates of thyroid hormone synthesis and secretion.
- The thyroid secretes 80 $\mu\text{g}/\text{day}$ in the form of T3 and T4.
- 40 $\mu\text{g}/\text{day}$ diffuses back into the extracellular fluid (ECF).
- Circulating T3 and T4 are metabolized in the liver and other tissues, with the release of a further 60 μg of I^- per day into the ECF.
- Some thyroid hormone derivatives are excreted in the bile, and some of the iodine in them is reabsorbed (enterohepatic circulation)
- Net loss of I^- in the stool of approximately 20 $\mu\text{g}/\text{day}$.



Outline of thyroid hormone synthesis

1. *Synthesis of thyroglobulin and its extrusion to the follicle lumen*
2. *Iodide Uptake (Iodine trapping)*
3. Oxidation of I⁻ to I₂ Ion.
4. Organification of thyroglobulin
5. Formation of MIT and DIT
6. Coupling of DIT and MIT to form of T₃ and T₄
7. *Endocytosis of thyroglobulin to thyrocyte*
8. *Hydrolysis and release of T₃ and T₄*
9. *deiodination of residual MIT and DIT*
10. *Recycling of tyrosine and I*
11. *Peripheral Conversion Of T₄ To T₃*



Iodine transport (trapping and organification)

- **Na⁺/I⁻ symport** : protein transport for iodide uptake from plasma to thyroid cells. (Iodine trapping)
- Iodide pump **concentrates iodide to about 30% times** more in cells than in plasma can be increased to 250 times by TSH.
- Iodide **trapping** is mainly influenced by **TSH level**.
- **Iodide (I⁻¹) is converted into Iodine (I⁰).**
- **This occurs at the apical surface of thyrocyte by the enzyme thyroid peroxidase (TPO).**
- *Hashimoto disease autoimmune antibodies against TPO are formed impairing thyroid hormone synthesis Anti-TPO antibodies).*

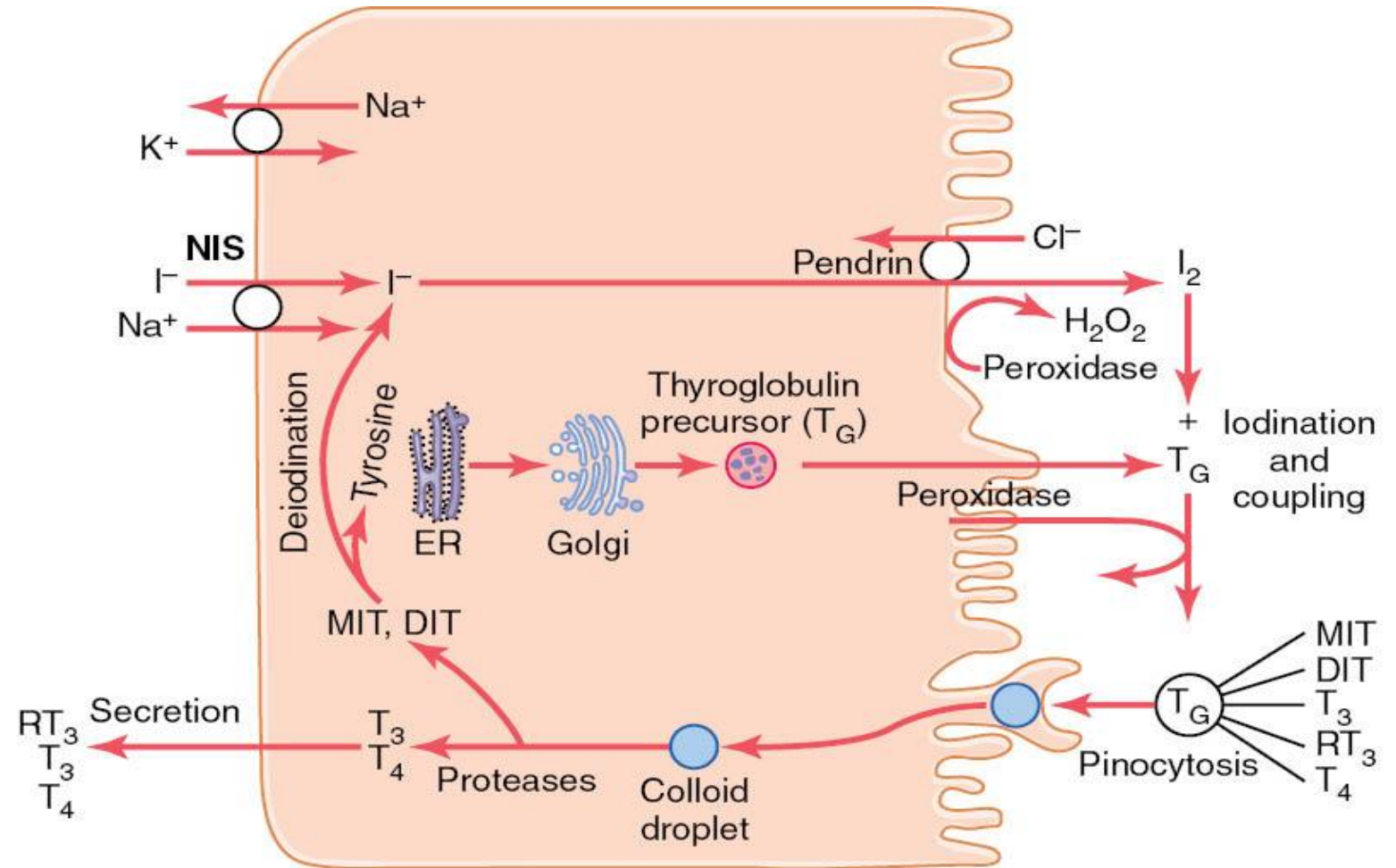


Iodine transport and metabolism

- Perchlorate is a contaminant that can be found in drinking and groundwater, and occasionally in cow's milk.
- Thiocyanate ions, perchlorate ions, and nitrate ions inhibit cause competitive inhibition of iodide transport into the cell—that is, inhibition of the iodide-trapping
- Ingestion of high levels of iodine , as with consumption of well water, can lead to inhibition of iodine transport into the follicular cells. (**Wolff–Chaikoff effect**)
- Thiouracil and ***propylthiouracil*** inhibit iodine organification.
- Severe iodine deficiency of the mother may lead to insufficient thyroid hormone synthesis in both mother and fetus resulting in developmental brain injury.
- Excess iodine supplementation may inhibit fetal thyroid function, leading to hypothyroidism (iodine toxicity).
- Iodides in high concentrations decrease all phases of thyroid activity, they slightly decrease the size of phases of thyroid activity, they slightly decrease the size o the gland
- For this reason, iodides are frequently administered to patients for 2 to 3 weeks before surgical removal of the thyroid gland to decrease the necessary amount of surgery, and especially to decrease the amount of bleeding.

Thyroid cellular mechanisms for iodine transport, thyroxine and triiodothyronine formation, and thyroxine and triiodothyronine release into the blood.

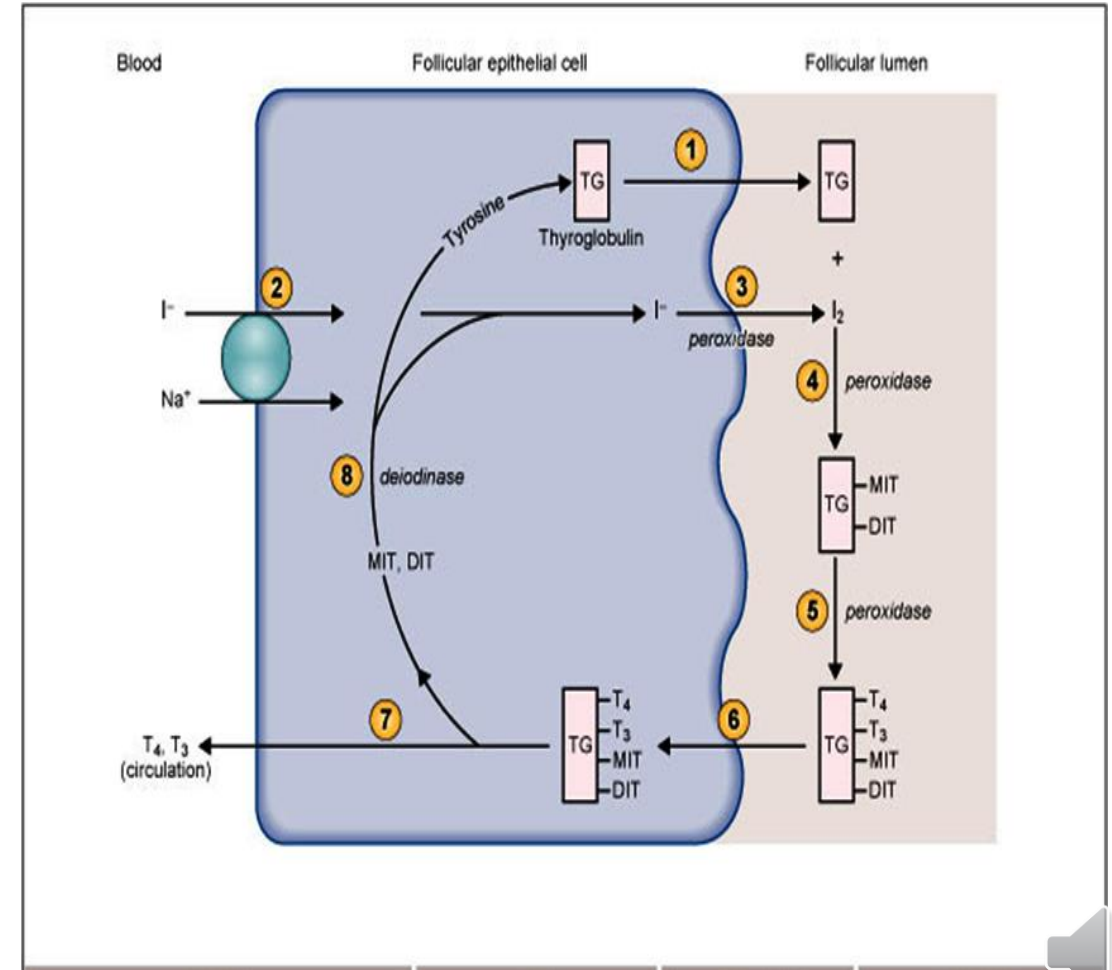
Cl⁻/I⁻ exchanger known as **pendrin**.
This protein was first identified as the product of the gene responsible for the Pendred syndrome, which causes thyroid dysfunction and deafness.



Thyroid cellular mechanisms for iodine transport, thyroxine and triiodothyronine formation, and thyroxine and triiodothyronine release into the blood.

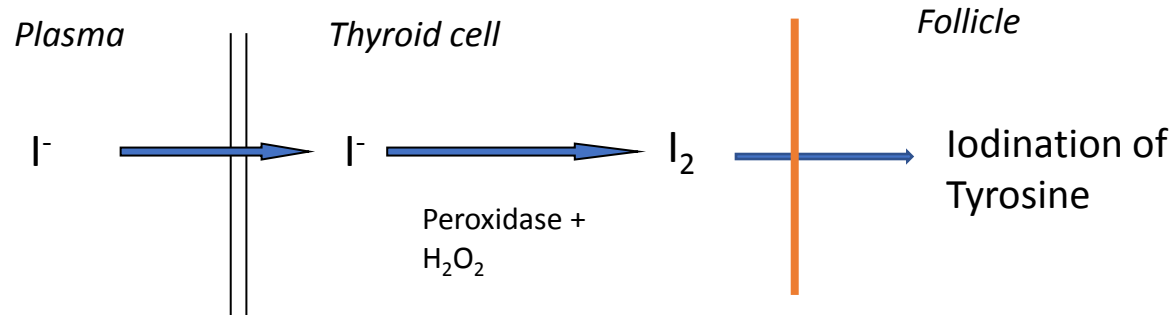
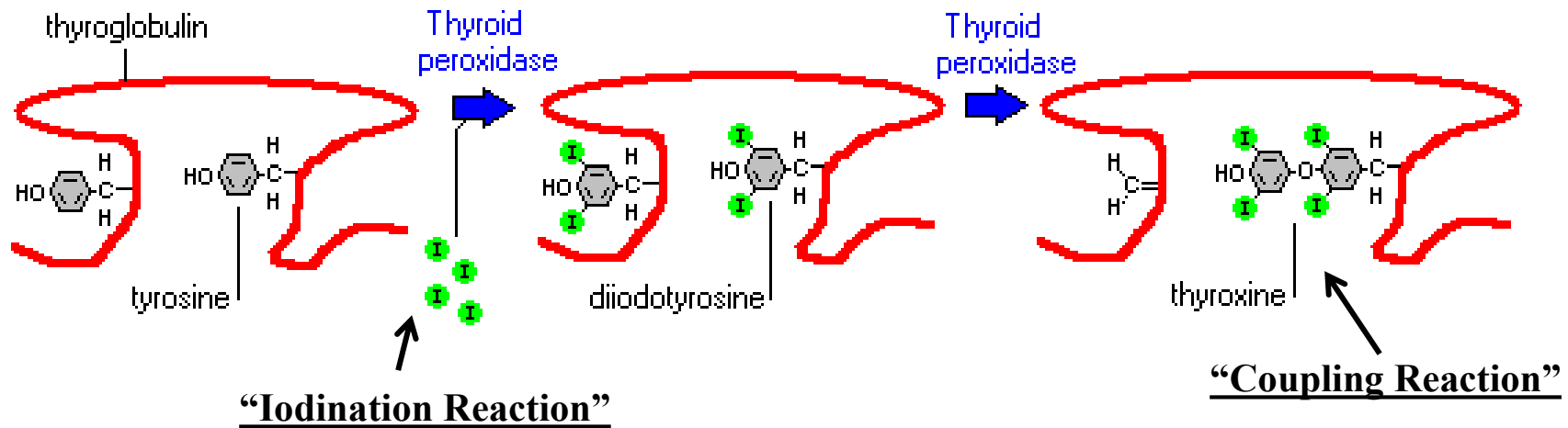
Event	Site	Enzyme	Inhibitor
1 Synthesis of TG; extrusion into follicular lumen	Rough ER, Golgi apparatus		
2 Na^+ - I^- cotransport	Basal membrane		Perchlorate, thiocyanate
3 Oxidation of $\text{I}^- \rightarrow \text{I}_2$	Apical (luminal) membrane	Peroxidase	PTU
4 Organification of I_2 into MIT and DIT	Apical membrane	Peroxidase	PTU
5 Coupling reaction of MIT and DIT into T_3 and T_4	Apical membrane	Peroxidase	PTU
6 Endocytosis of TG	Apical membrane		
7 Hydrolysis of T_4 and T_3 ; T_4 and T_3 enter circulation	Lysosomes	Proteases	
8 Deiodination of residual MIT and DIT Recycling of I^- and tyrosine	Intracellular	Deiodinase	

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MIT / DIT formation

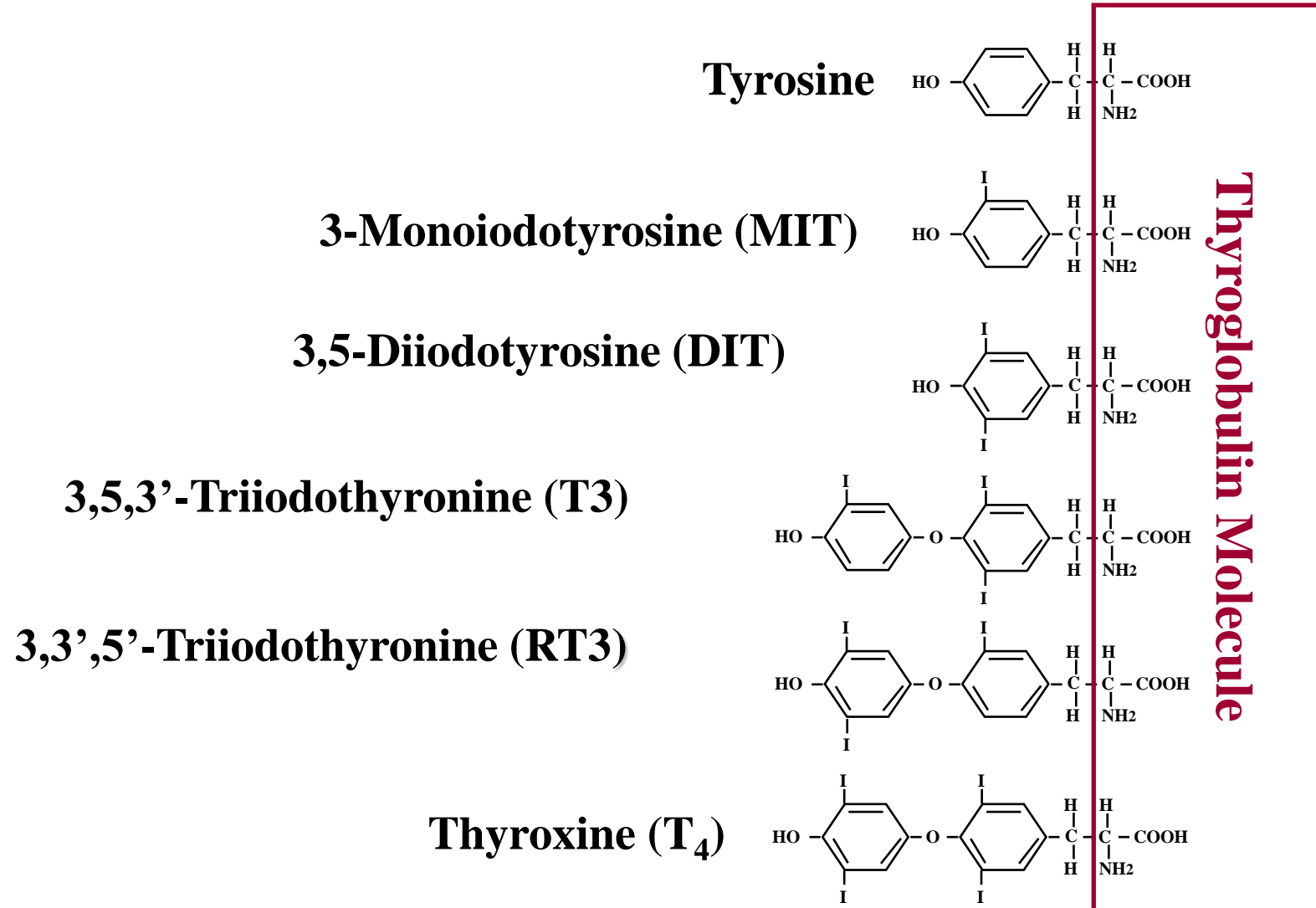
- Iodine coupled to Thyroglobulin (made by ER and Golgi, MW 335000, composed of 70 tyrosine aminoacids)
 - Monoiodotyrosine (Tg + one I)
 - Diiodotyrosine (Tg + two I)
- Stimulated by TSH
 - MIT + DIT = T₃
 - DIT + DIT = T₄



Finally, each TG molecule contains up to 30 thyroxine's & few T₃ (organization of TG)



Binding of THs & Precursors to TG During Hormone Synthesis

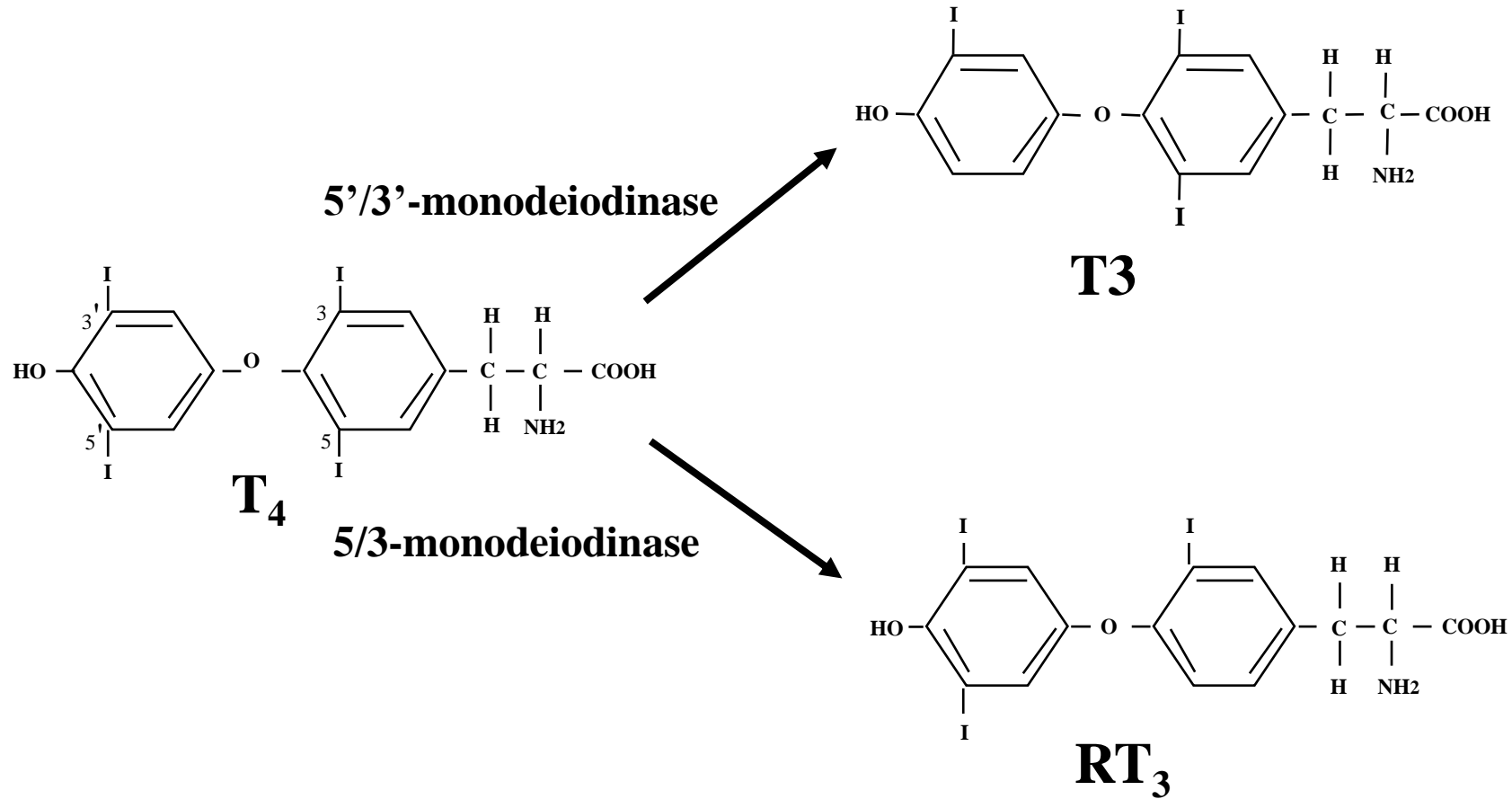


Storage of Thyroglobulin and thyroid hormones

- The thyroid gland store large amounts of hormone
- After synthesis of the thyroid hormones Each thyroglobulin molecule contains up to 30 thyroxine molecules and a few triiodothyronine molecules.
- In this form, the thyroid hormones are stored in the follicles.
- The stored amount is sufficient to supply the body with its normal requirements of thyroid hormones for 2 to 3 months.
- Therefore, when synthesis of thyroid hormone ceases, the physiological effects of deficiency are not observed for several months.
- Some of the thyroglobulin in the colloid enters the thyroid cell by *endocytosis* after binding to *megalin*, a protein located on the lumen membrane of the cells.
- The megalin-thyroglobulin complex is then carried across the cell by *transcytosis* to the basolateral membrane, where a portion of the megalin remains bound to thyroglobulin and is released into the capillary blood.



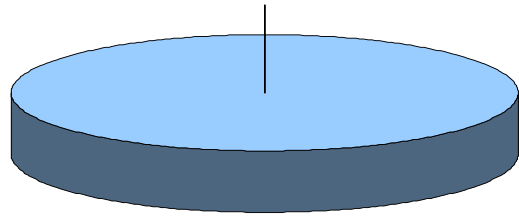
Metabolism of Thyroxine by Deiodination



Thyroid hormones metabolism

- T4 and T3 are deiodinated in the liver, the kidneys, and many other tissues.
- These deiodination reactions catabolize the hormones, also to provide a local supply specifically of T3, the primary mediator of the physiologic effects of thyroid secretion.
- One third of the circulating T4 is normally converted to T3 in adult humans
- 45% is converted to RT3.
- only about 13% of the circulating T3 is secreted by the thyroid while 87% is formed by deiodination of T4;
- similarly, only 5% of the circulating RT3 is secreted by the thyroid and 95% is formed by deiodination of T4.
- There is marked differences in the ratio of T3 to T4 occur in various tissues.
- Two tissues that have very high T3/T4 ratios are the pituitary and the cerebral cortex, due to the expression of specific deiodinases, (Three different deiodinases act on thyroid hormones: D1, D2, and D3.





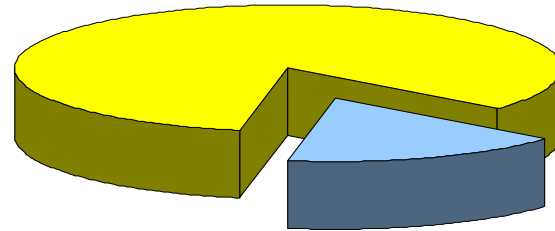
T₄
80 μg/day



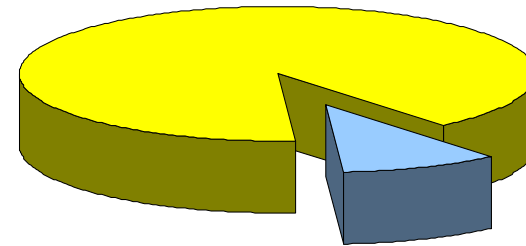
Secreted by thyroid



Deiodination of T₄ in peripheral tissues



T₃
31 μg/day



RT₃
38 μg/day



Daily secretion of thyroid hormones and Duration of action

- About 93 percent of the thyroid hormone released from the thyroid gland is normally thyroxine
- 7 percent is triiodothyronine.
- During the ensuing few days, about one half of the thyroxine is slowly deiodinated to form additional triiodothyronine.
- Therefore, the hormone finally delivered to and used by the tissues is mainly triiodothyronine
- Thyroid Hormones
- Have Slow Onset and Long Duration of Action
- T4 latent period few days , Maximum reached at 12 days
- The actions of triiodothyronine occur about four times as rapidly as those of thyroxine, with a latent period as short as 6 to 12 hours and maximal cellular activity occurring within 2 to 3 days.
- Most of the latency and the 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.



Transport Proteins of Thyroid hormones

Transport Protein	Principle Hormone Transported
Specific Thyroxine binding globulin (TBG)	Thyroxine, triiodothyronine
Nonspecific Albumin	Most steroids, thyroxine, triiodothyronine
Transthyretin (prealbumin)	Thyroxine, some steroids



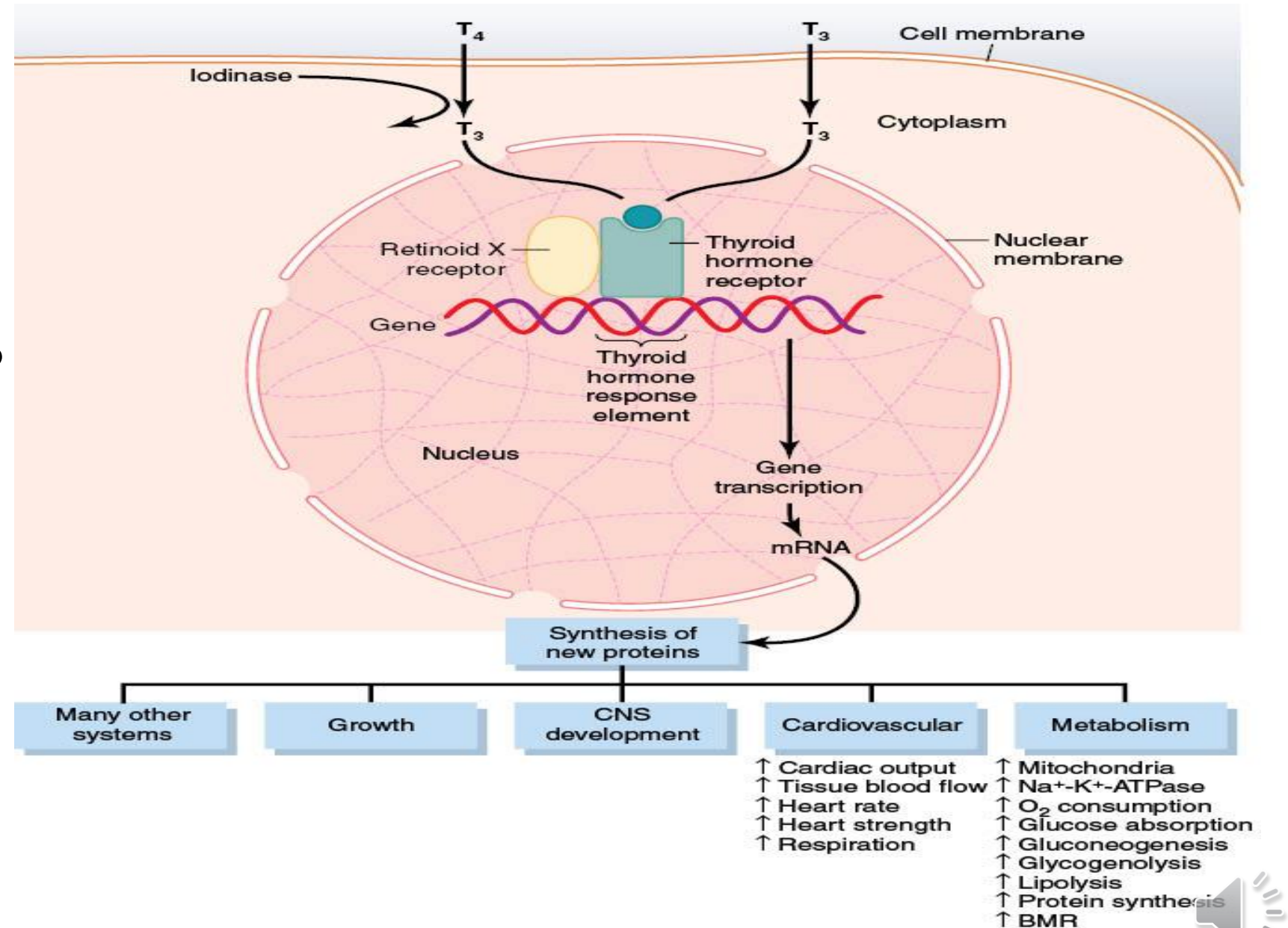
Binding of T3 and T4

- In the circulation, most of the T3 and T4 is bound to thyroxine-binding globulin (TBG).
 - In hepatic failure, TBG levels decrease, leading to a decrease in total thyroid hormone levels, but normal levels of free hormone.
 - In pregnancy, TBG levels increase, leading to an increase in total thyroid hormone levels, but normal levels of free hormone (i.e., clinically, euthyroid).
- Conversion of T4 to T3 and reverse T3 (rT3)
 - In the peripheral tissues, T4 is converted mainly to T3 or rT3 by iodinase
 - T3 is more biologically active than T4.
 - rT3 is inactive



Mechanism of thyroid hormone activation of target cells

Most of thyroxin is converted into T3. 90% of thyroid H molecules that bind with the receptors (Intracellular) is T3, 10% is T4.



Effects of thyroid hormones on growth

Growth

- Attainment of adult stature requires thyroid hormone.
- Thyroid hormones act synergistically with growth hormone and somatomedins to promote growth
- in children. thyroid hormone appears to be permissive or act synergistically with growth hormone or growth factors acting directly on bone

bone formation

- Thyroid hormones stimulate **bone maturation** as a result of ossification and fusion of the growth plates.
- In thyroid hormone deficiency, bone age is less than chronologic age.



CNS development

- Thyroid hormones are *critical* for development during the fetal and immediate post-natal period.
- They regulate
 - neuronal proliferation
 - differentiation ,myelinogenesis
 - synapse formation
- Thyroid hormone deficiency causes irreversible mental retardation
- a brief perinatal period when thyroid hormone replacement therapy is helpful
- . Cerebral cortex basal ganglia, and cochlea are most affected Consequently, thyroid hormone deficiency during prenatal or postnatal development causes **mental retardation**, motor rigidity, and deafness



Congenital Hypothyroidism

Congenital cretinism : **Thyroid hormone deficiency present at birth**

- Fetal thyroid dysgenesis
- Fetal hypopituitary hypothyroidism
- Inborn errors of thyroid hormone synthesis
- Maternal iodine deficiency
- Maternal antithyroid antibodies that cross the placenta
- **Excess iodine exposure during gestation** : use of an iodine-based medication like the antiarrhythmic drug amiodarone by the mother



Congenital hypothyroidism

- Most newborns with congenital hypothyroidism do not have any signs or symptoms of the condition during the first week
- This is due to the transplacental transfer of maternal T4 in utero
- Signs and symptoms of severe congenital hypothyroidism in some neonate
- Lethargy sleeps most of the time
- slow movement
- a hoarse cry
- persistent constipation.
- May find a puffy face, poor muscle strength, and a large tongue
- Distended abdomen and larger than normal fontanelles (soft spots) on the head.



Congenital hypothyroidism

- Abnormalities rapidly develop in nervous system maturation, which are irreversible and result in mental retardation
- Prepubertal bone growth, including bone ossification, are retarded in the absence of thyroid hormones
- Bone age does not match chronological age
- Infantile face morphological feature
- Disproportionate rate of growth, the soft tissues are likely to enlarge excessively, giving the child with cretinism an obese and short appearance.



Congenital hypothyroidism



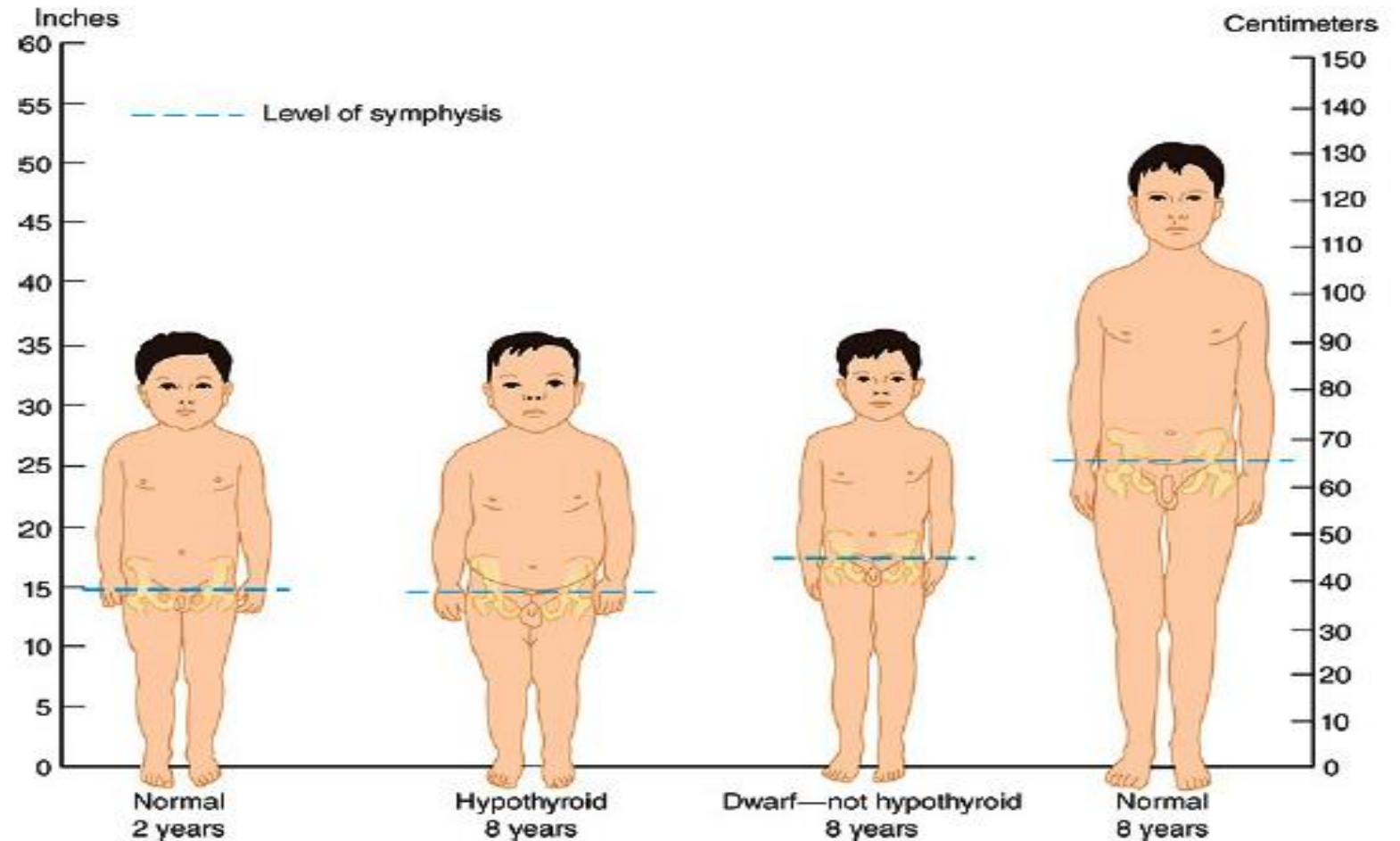
Dr Navneen Kumar Cheri
S. V. Medical College, Tirupati



Normal and abnormal growth

Children who are hypothyroid from birth or before are called **cretins**.

They are dwarfed and mentally retarded.



Normal; 6
years old



A

Cretin



B

Normal



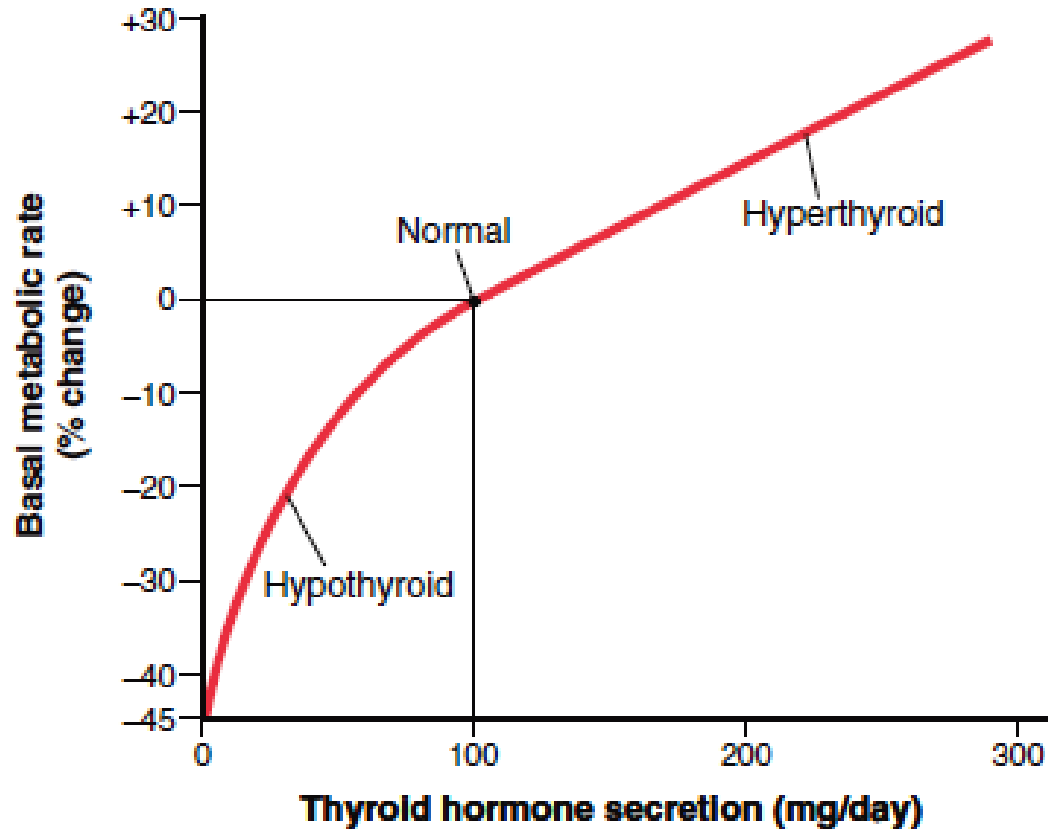
C

Cretin



Effects of thyroid hormones on Basal Metabolic Rate (BMR) (CALORIGENIC ACTION)

- **Increase O₂ consumption and BMR:** in all tissues except adult brain, testes, uterus, lymph nodes, spleen, and anterior pituitary
- **increases the synthesis of Na⁺, K⁺-ATPase** and consequently increases O₂ consumption related to Na⁺–K⁺ pump activity.
- Increases metabolism of the fatty acids they mobilization of fatty acids



Metabolic effects of thyroid hormones

- Glucose absorption from the gastrointestinal tract is increased.
- **Glycogenolysis, gluconeogenesis, and glucose oxidation** (driven by demand for ATP) are increased.
- Lipolysis is increased.
- Protein synthesis and degradation are increased.
- The overall effect of thyroid hormone is **catabolic**



Effects of thyroid hormone Stimulation of Carbohydrate Metabolism

- Increase glucose uptake by cells
- enhanced glycolysis and gluconeogenesis.
- increased rate of glucose absorption from the gastrointestinal tract.
- increased insulin secretion with its resultant secondary effects on carbohydrate metabolism
- In hyperthyroidism, therefore, the plasma glucose level rises rapidly after a carbohydrate meal, sometimes exceeding the renal threshold. However, it falls again at a rapid rate.
- All these effects probably result from the overall increase in cellular metabolic enzymes caused by thyroid hormone.



Effects of thyroid hormone on fat metabolism.

- Mobilization of lipids from fat tissue
- increases the free fatty acid concentration in the plasma
- Accelerates the oxidation of free fatty acids

- **EFFECTS ON CHOLESTEROL .**
- Decrease Cholesterol, Triglycerides and Phospholipids in plasma.
- *Mechanism*: increase formation of LDL receptors in the liver leads to secretion of LDL Cholesterol in Bile



Protein Metabolism

- In physiologic doses it is anabolic while in hyperthyroidism it is catabolic.
- Increase levels T3 increases BMR, causing negative nitrogen balance and decrease body weight if food intake is not adequate
- Decrease Thyroid hormone increases mucus like material consisting of protein complexed with hyaluronic acid and chondroitin sulphate in skin and water retention (**Myxedema**)
- In hypothyroid children, small doses of thyroid hormones cause a positive nitrogen balance because they stimulate growth, but large doses cause protein catabolism similar to that produced in the adult



EFFECTS ON SKELETAL MUSCLE

- Muscle weakness occurs in most patients with hyperthyroidism (**thyrotoxic myopathy**)
- The muscle weakness may be due in part to increased protein catabolism.
- Hypothyroidism is also associated with muscle weakness, cramps, and stiffness.



CNS effects in the adult

- **Hypothyroidism in adults:** *lack of energy consequently leads to*
 - *slowness of speech*
 - *impaired memory and somnolence,*
- Loss of interest and initiative, slowing mental processes.
- This eventually leads into dementia or madness like personality (**myxoedema madness**).
- *Conduction velocity in peripheral nerves is slowed and reflex time increased. For example, **delayed tendon reflexes (Hyporeflexia)***



CNS Effects

Hyperthyroidism in adults

- Hyperexcitability, irritability, restlessness, and exaggerated responses to environmental stimuli
- Increase intensity of tendon reflexes (Hyperreflexia)
- Emotional instability → psychosis, anxiety, and paranoia.
- Insomnia or unable to sleep Likely due to increase responsiveness to catecholamines of RAS and increased excitability of the neural synapses.



Cardiovascular vascular effects of thyroid hormone

Thyroid hormone increase O_2 consumption leads into metabolic excessive metabolic end products. slight rise in body temperature. This lead to

- an increase in heart rate, stroke volume and cardiac output.
- The increased myocardium strength likely to be due
 - The increased enzymatic activity caused by increased thyroid hormone production
 - increase responsiveness catecholamines
- Total peripheral resistance decreases because of cutaneous vasodilation.



Cardiovascular vascular effects of thyroid hormone

- Prolonged excess thyroid hormone (thyrotoxicosis) can cause **heart failure and cardiac decompensation**
- Cardiac decompensation and Myocardial Failure is secondary to
 - load imposed on the heart by the increase in cardiac output.
 - Excess secretion of thyroid hormones Increase protein catabolism depress myocardium contractility
- Excessive thyroid hormone causes tachycardia and palpitation



Changes in blood pressure in changes in thyroid disorders

■ **Hyperthyroidism:**

- **mean arterial pressure** is normal.
- The systolic BP is increased (10-15 mmHg) because of increased cardiac output
- diastolic pressure is reduced due to decreases TPR
- Pulse pressures often increased, with the systolic pressure elevated 10 to 15 mm Hg
- diastolic pressure reduced a corresponding amount *.(wide pulse pressure)*

■ ***Hypothyroidism***

- β -adrenergic synthesis is impaired
- α -adrenergic activity may predominate
- Increased TPR causing \uparrow BP.



Thyroid hormone and sympathetic nervous system activity

- T3 induces synthesis of *β -adrenergic receptors*. it up-regulates b-adrenergic receptors in the heart.
- Therefore, a useful adjunct therapy for hyperthyroidism is treatment with a β -adrenergic blocking agent, such as propranolol ever hyperthyroidism .
- Signs of *hyperthyroidism* which reflects increased β -adrenergic activity:
 - Tachycardia (increased heart rate)
 - \uparrow Cardiac output
 - Wide pulse pressure (High systolic and low diastolic).
 - anxiety
- During thyroid storm, an individual's heart rate, blood pressure, and body temperature can soar to dangerously high levels. Without prompt, aggressive treatment, thyroid storm is often fatal.



Effect of Thyroid Hormone on Sexual Function

- a great excess of the hormone sometimes causes impotence.
- In women, lack of thyroid hormone often causes *menorrhagia* and *polymenorrhea*—that is, excessive and frequent menstrual bleeding, respectively.
- In other women a lack of thyroid hormone may cause irregular periods and occasionally even *amenorrhea*



Thyroid and sexual functions

- Hypothyroidism in women, as in men, is likely to decreased libido.
- Women with hyperthyroidism, *oligomenorrhea* (greatly reduced bleeding) is common, and occasionally amenorrhea occurs.
- The action of thyroid hormone on the gonads probably results from a combination of direct metabolic effects on the gonads
- as well as excitatory and inhibitory feedback effects operating through the anterior pituitary hormones controlling gonads



Other effects thyroid hormones

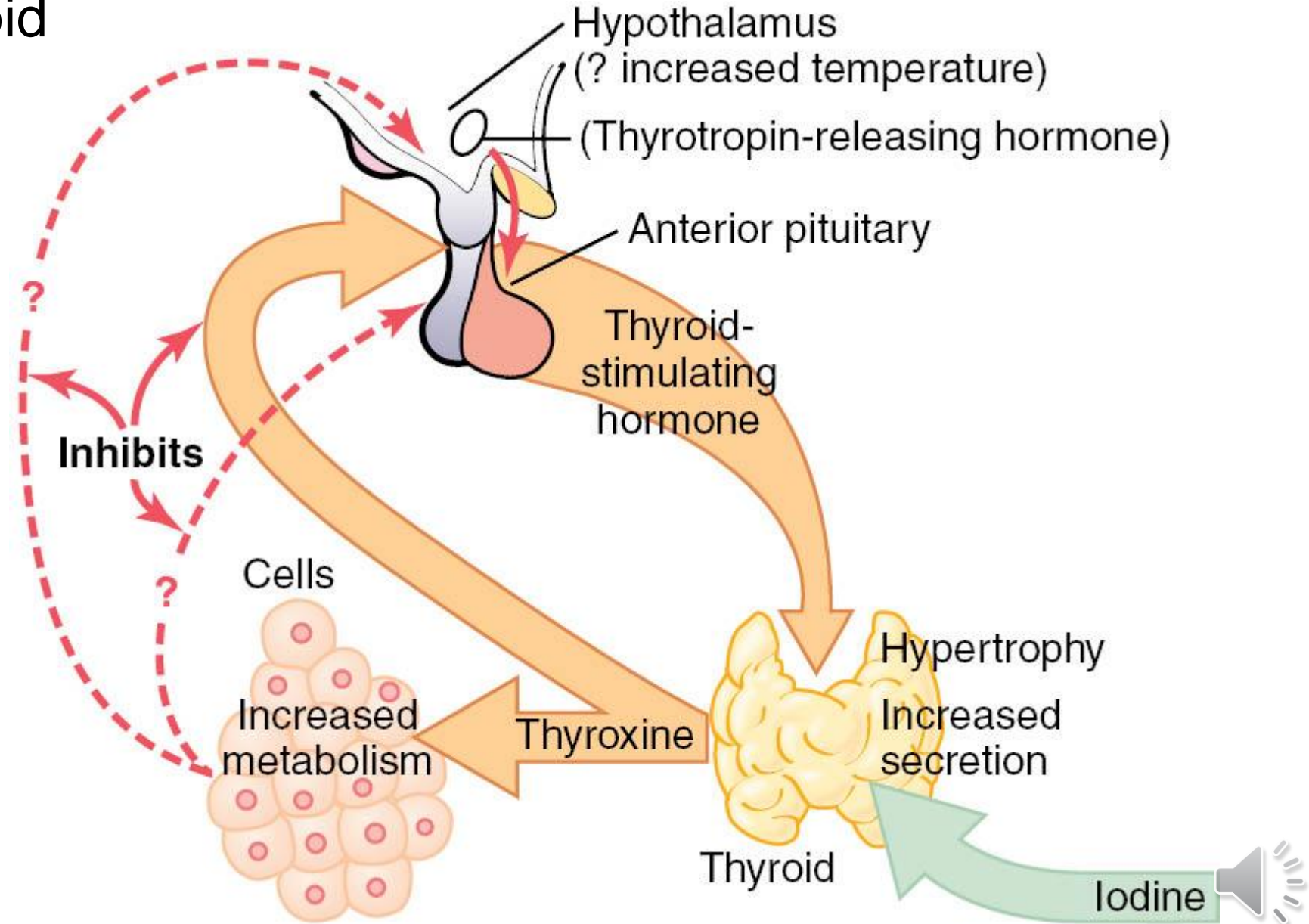
- **Respiration:** Increased O₂ metabolism, Increased CO₂ lead into increased rate and depth of respiration.
- **Digestive system** Thyroid hormones increase increased glucose rate of absorption from the gastrointestinal tract, GI motility and secretion
- **Increased Requirement for Vitamins requirements and utilization.** Because thyroid hormone increases the quantities of many bodily enzymes and because vitamins are essential parts of some of the enzymes or coenzymes
- **In hyperthyroidism**, the need for vitamins increases and vitamin deficiency syndrome may be precipitated
- **Carotene** is converted in the liver by thyroxine to vitamin A . In **hypothyroidism**, elevated serum carotene (**carotenemia**) causes **yellow tint**



Regulation of thyroid secretion.

Effects of increase or decrease
acres body temperature

Excitement and anxiety —
stimulate the sympathetic
nervous system—cause an acute
decrease in secretion of TSH



Effects of thyrotropin (TSH) and TRH on thyroid functions

- **TRH** is secreted by the hypothalamus and stimulates the secretion of TSH by the anterior pituitary.
- **TSH** increases both the synthesis and the secretion of thyroid hormones by the follicular cells via an **adenylate cyclase–cAMP** mechanism.
- *Rapidly induced TSH effects*
 - tends to rapidly increase (within minutes or an hour) all steps in the synthesis and degradation of thyroid hormones, including:
 - *Increased activity of the iodide pump (iodine trapping)*
 - Thyroglobulin synthesis and exocytosis into the follicular lumen
 - Pinocytotic reuptake of iodinated thyroglobulin back into the thyroid follicular cell
 - Secretion of T4 into the blood
 - *Increased proteolysis of the thyroglobulin*
 - *Increased iodination of tyrosine* to form the thyroid hormones
 - *Increased size and increased secretory activity of the thyroid cells*

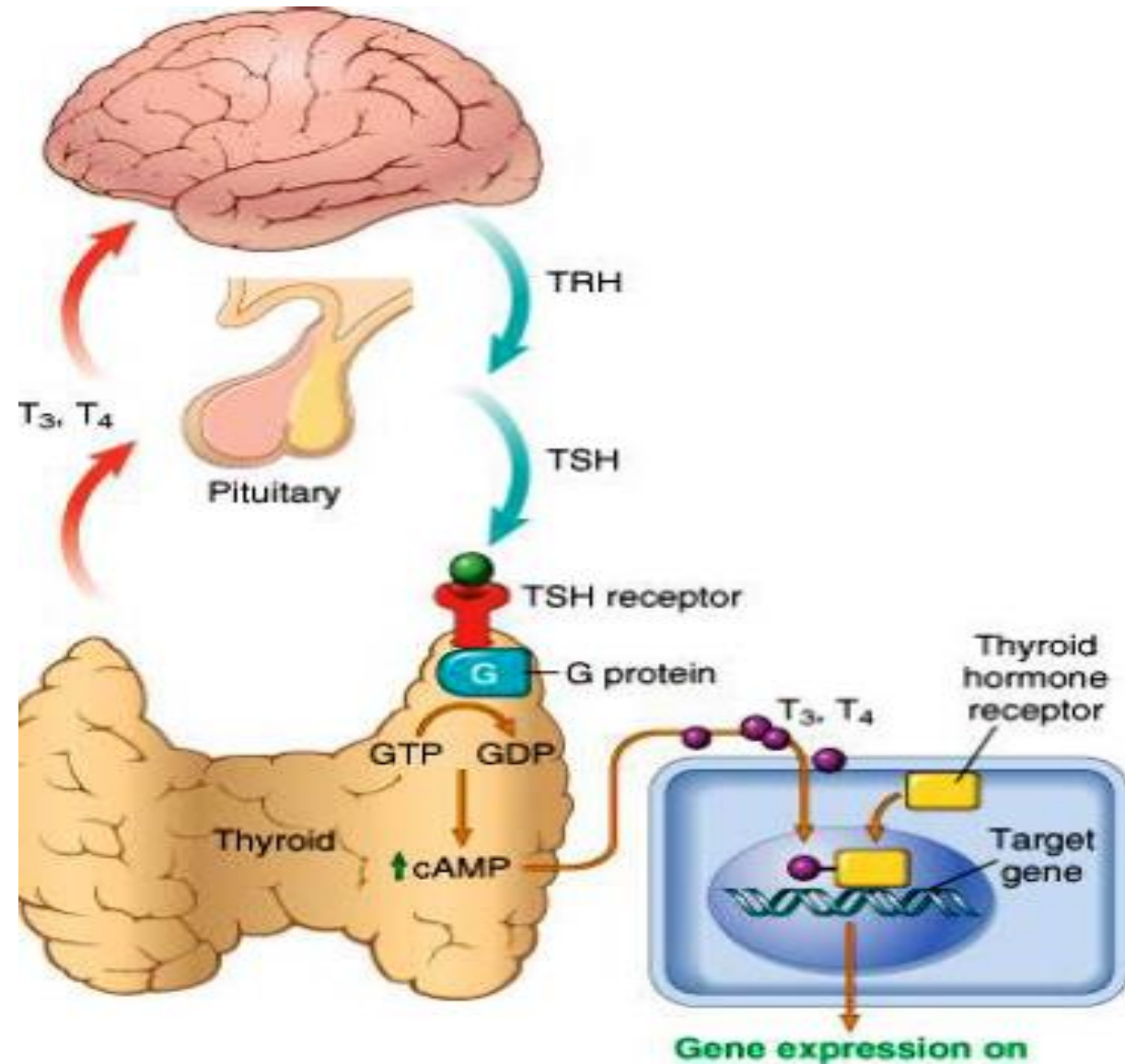


- *Slowly induced TSH effects on thyroid gland*
- Increased blood flow to the thyroid gland
- Chronic elevation of TSH causes **hypertrophy** of the thyroid gland or goiter



Mechanism of action of TSH and thyroid hormones

Cold environment



Changes in thyroid hormone secretion and feedback relation in several thyroid disorders

	T ₄	TSH	TRH
Primary hypothyroidism	↓	↑	↑
Pituitary hypothyroidism (secondary)	↓	↓	↑
Pituitary hyperthyroidism (secondary)	↑	↑	↓
Graves' disease (autoimmune)	↑	↓	↓



Thyroid-stimulating immunoglobulins

- are components of the immunoglobulin G (IgG) fraction of plasma proteins and are **antibodies to TSH receptors** on the thyroid gland.
- bind to TSH receptors and, like TSH, **stimulate the thyroid gland to secrete T3 and T4**.
- circulate in high concentrations in patients with **Graves disease**, which is characterized
 - high circulating levels of thyroid hormones
 - low concentrations of TSH (caused by feedback inhibition of thyroid hormones on the anterior pituitary).



Common Signs and Symptoms of Hypothyroidism

- Tiredness
- Loss of interest and pleasure
- Forgetfulness
- Dry coarse hair
- Puffy face and eyes
- Goiter
- Somnolence
- slurred speech
- Slow HR
- Dry skin
- Cold intolerance
- Weight gain without increase food intake
- Heavy menstruation!!!
- Constipation
- Brittle nails
- Slow deep tendon reflexes

Myxedema is a term generally used to denote severe hypothyroidism. Myxedema is also used to describe the dermatologic changes that occur in hypothyroidism and occasionally hyperthyroidism. In this setting, myxedema refers to deposition of mucopolysaccharides in the dermis, which results in development of an edematous appearance throughout the body called.



Common Signs and Symptoms of Hyperthyroidism

- Irritability, , nervousness, , hyperactivity, emotional instability,
- Difficulty Sleeping
- Nervousness
- Bulging Eyes (exophthalmos)
- Unblinking Stare
- Goiter
- Scanty Menstrual Periods!!!
- Increased Sweating
- Heat Intolerance
- Weight Loss
- Frequent Bowel Movements
- Warm, Moist Palms
- Fine Tremor of Fingers
- Palpitations
- widened pulse pressure
- Tachycardia at rest and during exercise



Tests of Thyroid Function

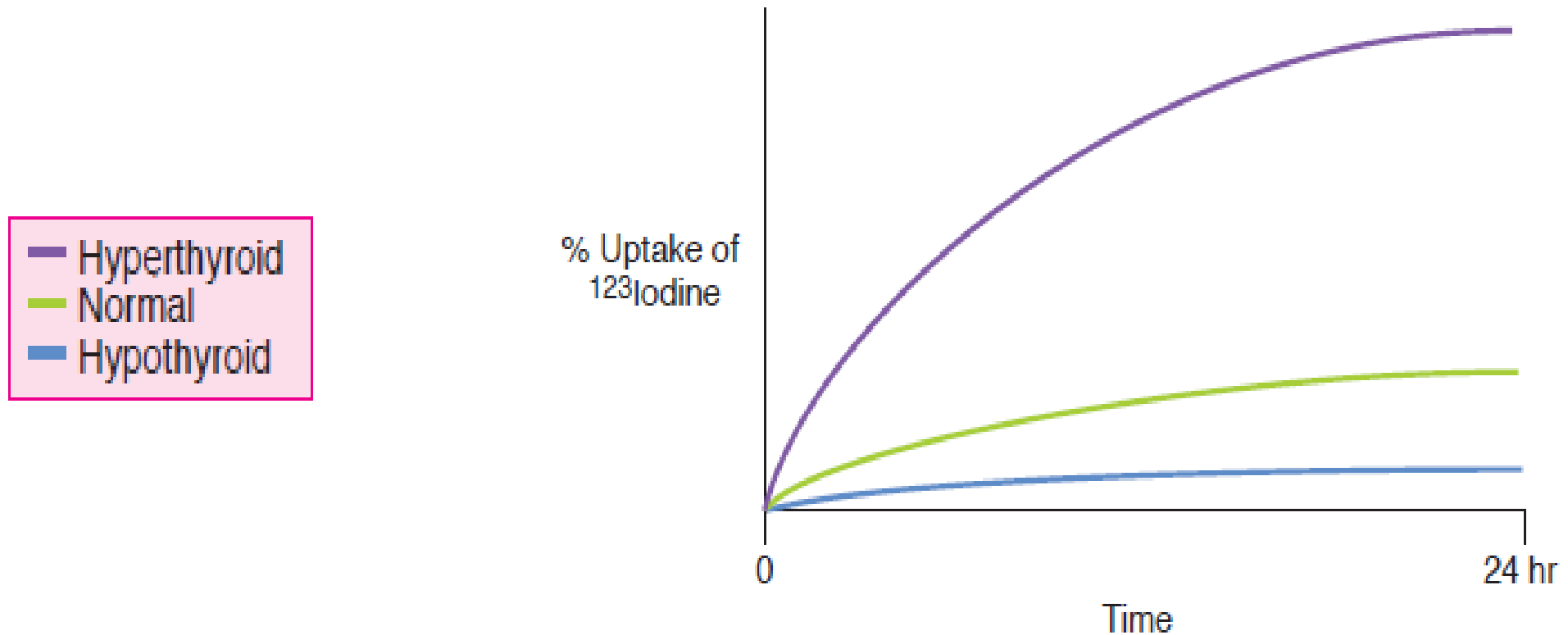
- Determining the serum TSH is the first step in evaluating thyroid function.
- Secondly, free T4 (T3) measurements confirm an initial conclusion based on the TSH measurement.
- Autoimmune thyroid diseases are sometimes detected by measuring circulating antibodies.
- **Thyroid peroxidase antibody (TPO)** : TPO antibodies, are elevated in Hashimoto's thyroiditis (hypothyroidism) and Graves' disease (hyperthyroidism).
- **Thyroid-stimulating immunoglobulins** are antibodies and have a similar action to TSH . They stimulate the TSH receptor on thyrocytes in Graves' disease.



Iodine uptake test

Relationship of Thyroid Function and Iodine Uptake

- The 24-hour iodine uptake by the thyroid is directly proportional to thyroid function.



Hyperthyroidism

- **Graves' Disease**

- Is an autoimmune condition leading to autonomous
- thyroid hormone secretion resulting from the stimulation of TSH receptor by TSH-like antibodies called ***thyroid-stimulating immunoglobulins (TSI)***.
- Clinically, about 40–50% of patients with hyperthyroidism present with protruding eyes and signs of hyperthyroidism mentioned previously
- Swelling of the orbit and eyes cause protrusion of the eyeball (***exophthalmos***)
- *exophthalmos* is caused by infiltration of lymphocyte and fibroblast of the extraocular tissues and muscles, and accumulation of hyaluronate a glycosaminoglycan produced by fibroblasts in the tissues and muscles of the eye .



Other cause of hyperthyroidism

- **Secondary hyperthyroidism TSH secreting tumor**
- Is due to increased thyroid hormone release by the thyroid gland in response to increased TSH levels derived from TSH-secreting pituitary adenomas
- TSH-secreting adenomas represent a very small fraction (<1%) of all pituitary adenomas and result in a syndrome of excess secretion of TSH.
- The hormonal profile is characterized by the inability to suppress TSH despite increased levels of free thyroid hormones (T3 and T4).
- **Thyroid Adenoma.**
 - Localized adenoma (a tumor) that develops in the thyroid tissue and secretes large quantities of thyroid
 - Thyroid hormone from the adenoma depresses the production of TSH by the pituitary gland.
 - Therefore , the secretion normal cells of the gland are inhibited



Primary Hypothyroidism

Hashimoto's thyroiditis

- Most common cause is, an autoimmune destruction of the thyroid with lymphocytic infiltration; ↑ TPO antibodies
- Hashimoto thyroiditis, autoimmune antibodies and infiltrating cytotoxic T cells ultimately destroy the thyroid.
- During the early stage the inflammation of the gland causes excess thyroid hormone secretion.
- Early stages have a diffusely enlarged thyroid progressing in the later stages to a smaller atrophic and fibrotic gland.
- ↑ TSH, ↓ FT4
- Inability to convert carotene to vitamin A may cause yellowing of the skin
- Slow thinking and lethargy; some patients have severe mental symptoms, dementia, or psychosis (“myxedema madness”)
- other signs and symptoms of hypothyroidism mentioned earlier



Additional causes of hypothyroidism

- Panhypopituitarism
- Severe iodine deficiency
- Failure to escape from the Wolff-Chaikoff effect following excessive iodine intake
- Rarely there can be resistance to thyroid hormone



- Patient with myxedema.



- Patient with exophthalmic hyperthyroidism. Note protrusion of the eyes and retraction of the superior eyelids. The basal metabolic rate was +40.



(Courtesy Dr. Leonard Posey.)



Goiter

- A goiter is simply an overall enlargement of thyroid and does not designate functional status.
- A goiter can be present in hypo-, hyper- state
- It can be associated with either decreased (iodine deficiency, Hashimoto's and Graves' disease)



(Courtesy Dr. Leonard Posey.)



Simple Goiter

If the dietary **intake of iodide is decreased** drastically, the **T3 and T4** synthesis will be **decreased**.

This will lead to decreased -ve feedback on the pituitary, leading to **increased production of TSH**, which causes the **thyroid to enlarge** (causing *endemic goiter*).



Clinical Correlation

- A premenopausal woman presents with palpitations and a history of weight loss over the past 6 months. In addition, she complains of increased irritability and anxiety, inability to sleep, and heat intolerance. Physical examination reveals **tachycardia** (pulse of 120 beats/min), **hypertension** (a blood pressure of 139/80 mm Hg), and a diffusely enlarged nontender thyroid gland. In addition, she has infrequent blinking and characteristic stare, sweaty hands, and tremor. Her serum TSH level is low, and the level of free thyroxine is increased. She is diagnosed with Graves' disease.
- Graves' disease accounts for 50–80% of cases of hyperthyroidism, affects approximately 0.5% of the population, and is more frequent in females than in males. The excess production of thyroid hormone in Graves' disease is the result of circulating IgG antibodies that bind to the TSH receptor on the thyroid gland, activating the G protein–coupled receptor. This excess stimulation of the receptor leads to follicular hypertrophy and hyperplasia, causing thyroid enlargement, as well as increases in thyroid hormone production.
- As a result of excess thyroid hormone production, the release of TSH is markedly suppressed via negative feedback. Clinical manifestations are the result of excess thyroid hormone activity. Treatment for Graves' disease includes antithyroid drugs (inhibitors of thyroid hormone synthesis), radioiodine ablation of the thyroid tissue, and surgical removal of the thyroid gland.

