Medical physiology

THYROID GLAND

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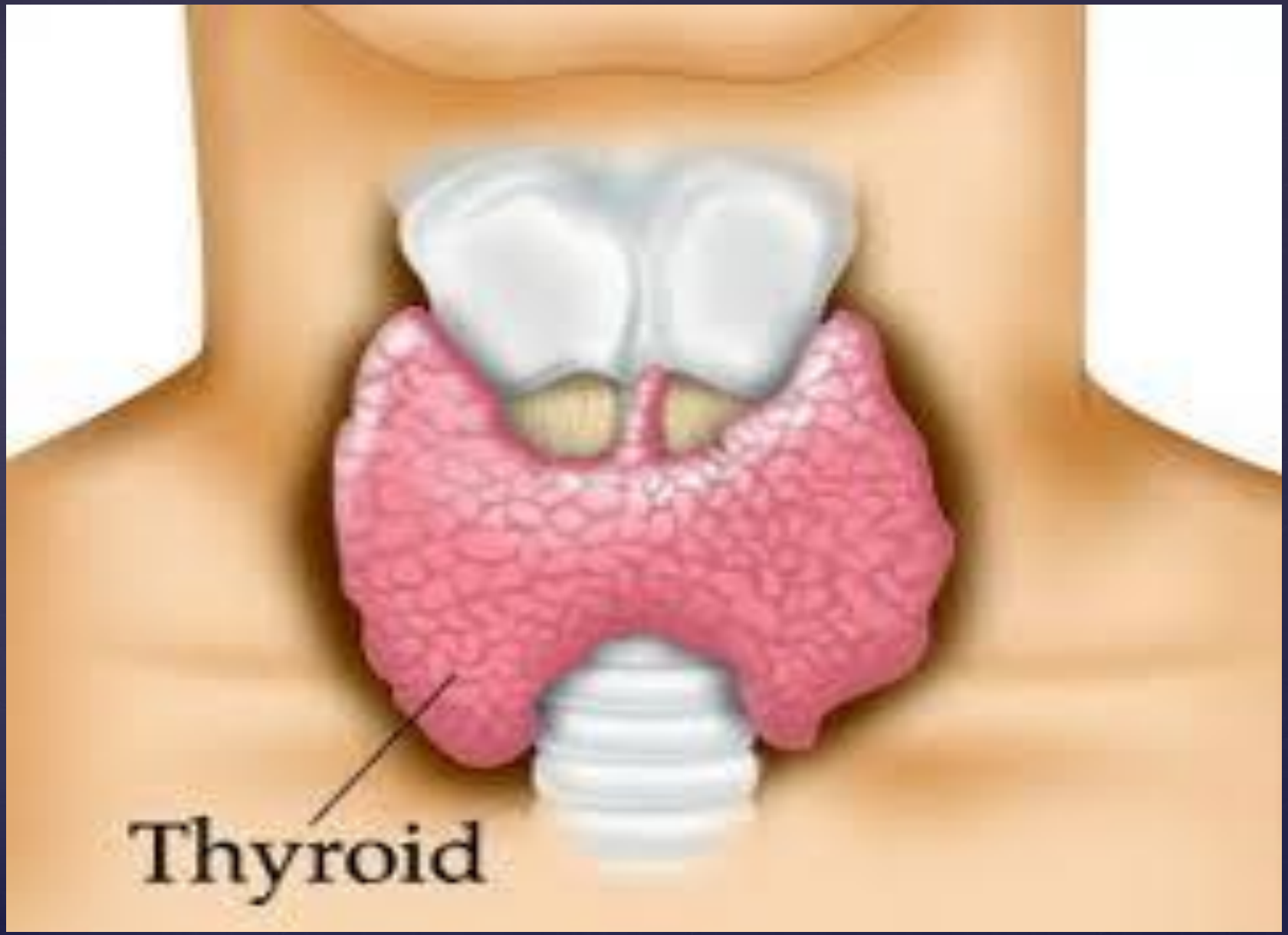
Lec 8

- After studying this lecture, you should be able to:

1. Describe the structure of the thyroid gland and how it relates to its function.
2. Define the chemical nature of the thyroid hormones and how they are synthesized.
3. Understand the critical role of iodine in the thyroid gland and how its transport is controlled.
4. Describe the role of protein binding in the transport of thyroid hormones and peripheral metabolism.
5. Identify the role of the hypothalamus and pituitary in regulating thyroid function.
6. Define the effects of the thyroid hormones in homeostasis and development.
7. Understand the basis of conditions where thyroid function is abnormal and how they can be treated

Thyroid Gland

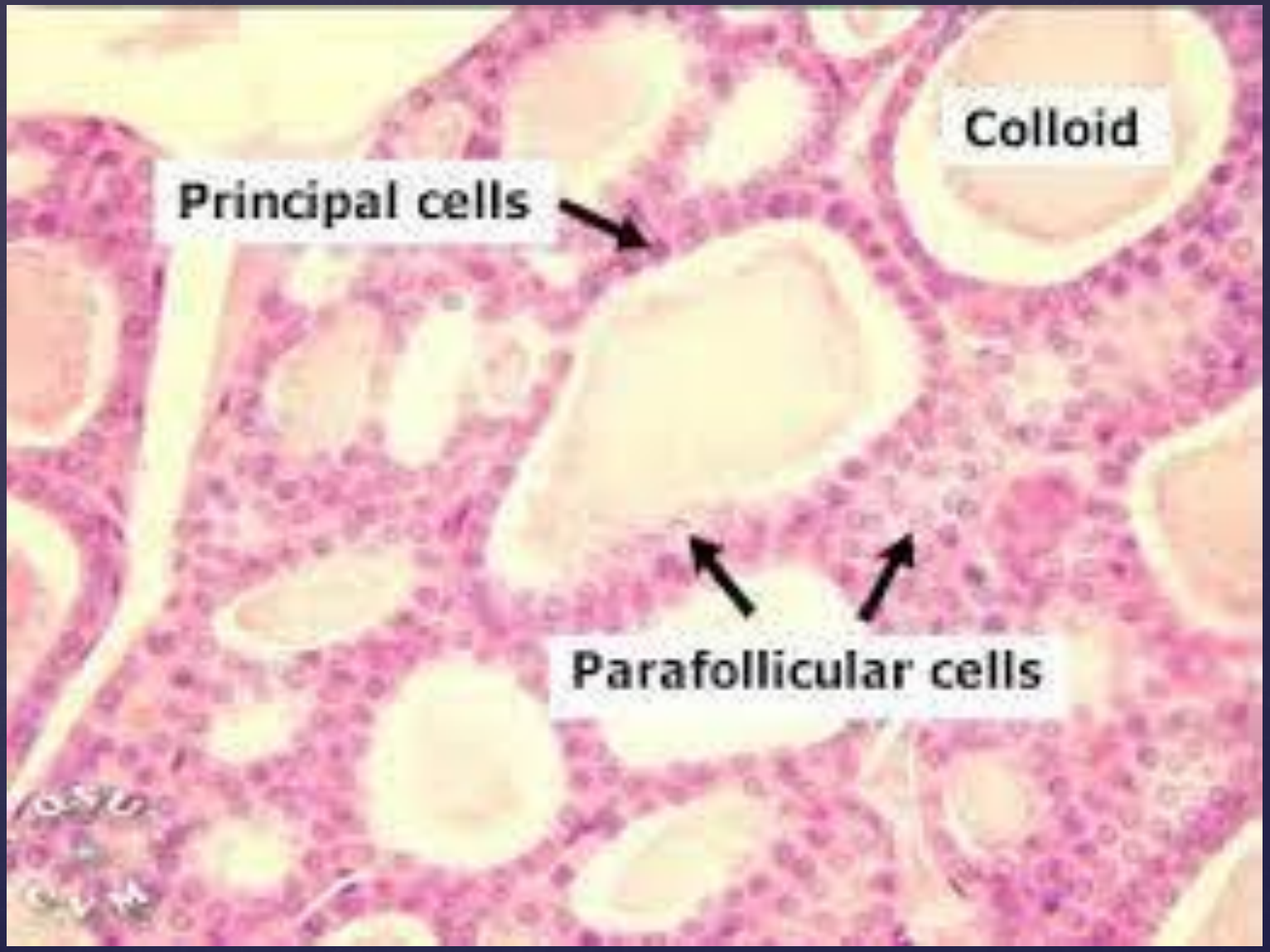
- The thyroid gland is a highly vascular endocrine gland that straddles the trachea in the front of the neck.
- It consists of two lateral lobes connected by a narrow isthmus that lies in front of the trachea. The gland weighs approximately 20 to 40 grams in adults, and its size is usually larger in females than in males.
- Embryologically, It develops from an invagination of the floor of the pharynx,. During its descent, it remains connected to the tongue by the thyroglossal duct, which usually disappears later; persistence of this duct may lead to a thyroglossal cyst in adults.



Thyroid gland

- **Histology of Thyroid gland:**

- The thyroid gland is made up of many follicles, each surrounded by cuboidal follicular cells. The center of each follicle contains colloid, rich in thyroglobulin, where thyroid hormones T_3 and T_4 are made and stored.
- Between follicles are parafollicular (C) cells, which secrete calcitonin to help regulate blood calcium levels.
- The thyroid is highly vascular, ensuring rapid hormone release into the bloodstream.


Colloid
Principal cells
Parafollicular cells

- **The Thyroid Gland Secretes Three Hormones:**

1. **Thyroxine (Tetraiodothyronine, T_4):**
    1. Represents about **90–93%** of the total thyroid hormone secretion.
    2. Serves mainly as a **prohormone**, converted to the more active T_3 in peripheral tissues.
2. **Triiodothyronine (T_3):**
    1. Accounts for about **7–10%** of thyroid hormone secretion.
    2. It is **3–5 times more biologically active** than T_4.
3. **Calcitonin:**
    1. Secreted by the **parafollicular (C cells)** of the thyroid gland.
    2. Plays a role in **calcium homeostasis**, by **decreasing blood calcium levels**

Thyroid Hormone Chemistry and Iodine Metabolism

- The thyroid gland mainly secretes **thyroxine (T_4)** and smaller amounts of **triiodothyronine (T_3)**.
- Both are **iodinated derivatives of tyrosine**, while small amounts of **reverse T_3 (rT_3)** are also found but are **biologically inactive**.
- **Reverse T_3** (rT_3) is an inactive form of thyroid hormone produced when T_4 is converted by type III deiodinase. It helps the body reduce metabolism during stress, illness, or fasting by lowering active T_3 levels.

Iodide Transport

- Iodide is actively transported into thyroid follicular cells via the Na^+/I^- symporter (NIS) on the basolateral membrane, driven by the Na^+/K^+-ATPase pump, allowing intracellular accumulation up to 40× plasma levels.
- Iodide then moves across the apical membrane into the follicular lumen through the Cl^-/I^- exchanger (pendrin), where hormone synthesis occurs.
- Pendrin mutations → Pendred syndrome (thyroid dysfunction + sensorineural deafness).

Iodine Homeostasis and Clinical Significance

- Iodine is vital for making thyroid hormones. The body needs about 150 µg/day, and most people get more through iodized salt.
- About 20% of blood iodide goes to the thyroid, while the rest (≈80%) is excreted by the kidneys.
- Both iodine deficiency and excess can reduce thyroid activity.

- **Thyroid Hormone Synthesis, Secretion & Transport**
- **Hormone Synthesis**
- Inside the thyroid follicle, iodide is oxidized to iodine by thyroid peroxidase (TPO) and attached to tyrosine residues on thyroglobulin (TG) — this is called organification that forming:
- **Monoiodotyrosine (**MIT) = one iodine added
- **Diiodotyrosine (**DIT) = two iodines added
- T_4 (thyroxine) = DIT + DIT
- T_3 (triiodothyronine) = MIT + DIT
- These steps all depend on TPO. The formed T_3 and T_4 stay stored in the colloid bound to TG, providing a 1–2 month reserve of thyroid hormone even if iodine intake stops.

- **Hormone Secretion:**
- When TSH stimulates the thyroid, the follicular cells take in colloid droplets (which contain thyroglobulin with stored T_3 and T_4).
- Inside the cell, enzymes break down thyroglobulin to release T_4 and T_3, which then enter the blood.
- Unused MIT and DIT are broken down by a special enzyme to recycle iodine.
- If this enzyme is missing, iodine is lost in urine, leading to iodine deficiency symptoms.

Transport in Blood

- T_4 and T_3 are lipid-soluble and circulate mostly bound to plasma proteins, forming a large reservoir that stabilizes hormone availability and prevents rapid tissue uptake.
- Only free (unbound) hormones are biologically active and provide negative feedback to the pituitary to regulate TSH secretion.
- **Major binding proteins include**:

1. **Thyroxine-binding globulin (TBG)**
2. **Transthyretin**
3. **Albumin**

- Normal plasma concentrations(total hormone levels, including both bound and free forms):

- **T_4:** ~8 μg/dL (103 nmol/L)
- **T_3:** ~0.15 μg/dL (2.3 nmol/L)

- Because only free hormones are metabolically active, **free T_4 and free T_3 levels** are the **most clinically useful** measures for assessing thyroid function.

Plasma Binding & Half-life of Thyroid Hormones

- Most thyroid hormones are protein-bound in plasma; only a tiny free part is active.
- T_4 binds more strongly to plasma proteins → slower action, longer half-life (~7 days)
- T_3 binds less strongly → faster action, shorter half-life (~1 day).
- Free hormones (FT_4 & FT_3) are the only forms that enter cells and act on tissues.

Fluctuations in Thyroid Hormone Binding:

- Changes in binding proteins affect total hormone levels, not thyroid function:
- When TBG increases, more T_4 and T_3 become protein-bound → total levels rise but free (active) hormones stay normal, so the person remains euthyroid.
- When TBG decreases, total hormone levels fall but free levels remain normal.
- TBG increases in pregnancy, estrogen therapy, and some drugs.
- TBG decreases with androgens, glucocorticoids, or chemotherapy.

Metabolism of Thyroid Hormones

- T_4 and T_3 are deiodinated mainly in the liver, kidneys, and other tissues.
- These reactions both break down hormones and produce local T_3, the active form.
- About 33%of circulating $T_4 \rightarrow T_3$, and ~45% $\rightarrow$ reverse T_3 (rT_3).
- Only ~13% of T_3 and ~5% of rT_3 come directly from the thyroid; the rest is made from T_4.
- Brain and pituitary have a high T_3/T_4 ratio due to strong local conversion.

Regulation of Thyroid Hormone Secretion

- The hypothalamus–pituitary–thyroid (HPT) axis controls thyroid activity through a negative feedback mechanism.
- The hypothalamus secretes thyrotropin-releasing hormone (TRH), which travels via the hypothalamo-hypophyseal portal system to the anterior pituitary, stimulating the release of thyroid-stimulating hormone (TSH).
- TSH, a glycoprotein hormone (α & β chains; half-life ≈ 60 min), acts via the cyclic AMP (cAMP) second-messenger pathway to regulate growth and function of the thyroid gland

Major Actions of TSH

- TSH stimulates every step of thyroid hormone formation and release:

1. Growth and increased number of follicular cells.
2. Enhanced iodide uptake, thyroglobulin synthesis, and iodination.
3. Coupling reactions to form T_3 and T_4.
4. Proteolysis of thyroglobulin → rapid release of T_3 and T_4 (within ~30 min).

- Feedback control circulating T_3 and T_4 inhibit further TRH release from the hypothalamus and TSH secretion from the pituitary, maintaining stable hormone levels (euthyroid state).

Functions of Thyroid Hormones:

- Thyroid hormones (T_3 and T_4) act on nearly all body tissues and play a vital role in metabolism, growth, and development. Their effects are mainly stimulatory, increasing oxygen consumption and energy production.

Effect on Basal Metabolic Rate (BMR)

- Thyroid hormones increase oxygen consumption and heat production in most tissues (calorigenic effect).
- BMR rises by 60–100% in hyperthyroidism and falls by 20–40% in hypothyroidism.

Protein Metabolism

- In normal levels, thyroid hormones enhance protein synthesis by increasing DNA transcription(leading to increased mRNA formation) and RNA translation(resulting in greater protein production).
- Excess hormone → protein breakdown (catabolism) → muscle weakness (thyrotoxic myopathy).
- Deficiency → sluggish muscles and delayed relaxation.

Carbohydrate Metabolism

1. Thyroxine Increases glucose absorption from the intestine.
2. Promotes cellular glucose uptake and glycogenolysis.
3. Stimulates gluconeogenesis in the liver.

Fat Metabolism

1. Mobilizes fat from adipose tissue → increases free fatty acids in blood.
2. Decreases plasma cholesterol, triglycerides, and phospholipids by enhancing hepatic LDL receptor activity and cholesterol excretion in bile.

- Hypothyroidism → ↑ plasma cholesterol → atherosclerosis.
- Hyperthyroidism → fatty liver due to increased fat turnover.

- **Vitamin Metabolism**
- Increases enzyme synthesis, thus increasing vitamin utilization(Since vitamins form essential parts of the enzymes) → may cause vitamin deficiency during hyperthyroidism
- **Thermogenesis**
  - Raises body temperature by increasing metabolic rate.
  - Hyperthyroidism: heat intolerance and sweating.
  - Hypothyroidism: cold intolerance.

Growth and Development

- Essential for normal growth in children; deficiency → growth retardation.
- Hyperthyroidism → causes accelerated skeletal growth → child becomes taller early , but bones mature and fuse prematurely (early epiphyseal closure).Therefore, final adult height may be reduced despite rapid early growth.
- Crucial for brain development during fetal and early postnatal life — deficiency → irreversible mental retardation (cretinism).

Body Weight

- Excess hormone: decreases body weight (fat loss).
- Deficiency: increases weight (fat accumulation).

Blood and Erythropoiesis

- Stimulates erythropoietin and increases blood volume.(Why????????)

Cardiovascular System

- Increases heart rate
- force of contraction, and cardiac output (β_1 receptor stimulation)
- Causes vasodilation due to increased tissue metabolism.
- May cause cardiac failure if prolonged hyperactivity (thyrotoxic heart).

Respiration:

- Secondary increase in rate and depth of breathing due to higher oxygen demand and CO_2 production

Gastrointestinal Tract

- Increases appetite, secretion, and motility.
- Hyperthyroidism: diarrhea.
- Hypothyroidism: constipation.

Central Nervous System

- Essential for normal neuronal development and function.
- Hyperthyroidism: nervousness, irritability, tremor, insomnia.
- Hypothyroidism: mental slowing, somnolence

Reproductive System

- Normal levels required for fertility.

- **In male :**
- Hypothyroidism → Low thyroid hormone levels reduce metabolic activity and testosterone synthesis in Leydig cells. This results in decreased libido and occasionally mild testicular atrophy
- Hyperthyroidism → Excess thyroid hormones increase the metabolic clearance rate of testosterone and promote peripheral conversion of testosterone to estradiol.
- This leads to impotence or erectile dysfunction, despite sometimes preserved libido.

➢ **In female**

- Low thyroid hormones lead to elevated TRH from the hypothalamus.
- TRH stimulates prolactin (PRL) secretion from the anterior pituitary.
- High prolactin inhibits GnRH release, causing reduced FSH and LH secretion → anovulation and menstrual disturbances.
- Hyperthyroidism
- Excess thyroid hormones accelerate the metabolism of estrogen and progesterone in the liver and decrease their plasma duration.
- They also alter ovarian responsiveness to gonadotropins.
- These changes cause oligomenorrhea (infrequent menses) or amenorrhea.