

THYROID HORMONES – An Overview

SCHOOL OF MEDICINE AND HEALTH SCIENCES

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DISCIPLINE OF BIOCHEMISTRY AND MOLECULAR BIOLOGY

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What are the Thyroid Hormones?

- **Thyroid Hormones are:**
 - **Thyroxine** : {3,5,3',5' – Tetra-Iodothyronine} (**T4**)
 - **Tri-Iodothyronine**: {3,5,3' – Tri-Iodothyronine} (**T3**)
- **T4** contains Four Iodine atoms,
- **T3** contains Three Iodine atoms,
- **T3**: Biological active form of Thyroid hormones, because it binds to receptors and trigger end-organ effects;
- Thyroid hormones are unique because they contain the trace element **Iodine** for Biological activity;
- **Reverse T3**: {3,3',5'-Tri-Iodothyronine} (**rT3**):
 - Is the **Biological Inactive** form of Thyroid hormones;

How are Thyroid Hormones biosynthesized?

- Biosynthesis of Thyroid hormones occurs in the Thyroid gland (**Fig. 1**);
- Process involves:
 - Trapping of Iodide (I^-),
 - Iodination (Organification) of Tyrosine residues to form MIT & DIT on **Thyroglobulin (TG)**,
 - Coupling of DIT and MIT on TG to form Thyroid hormones;
- **The process can be separated into Two Major Stages;**

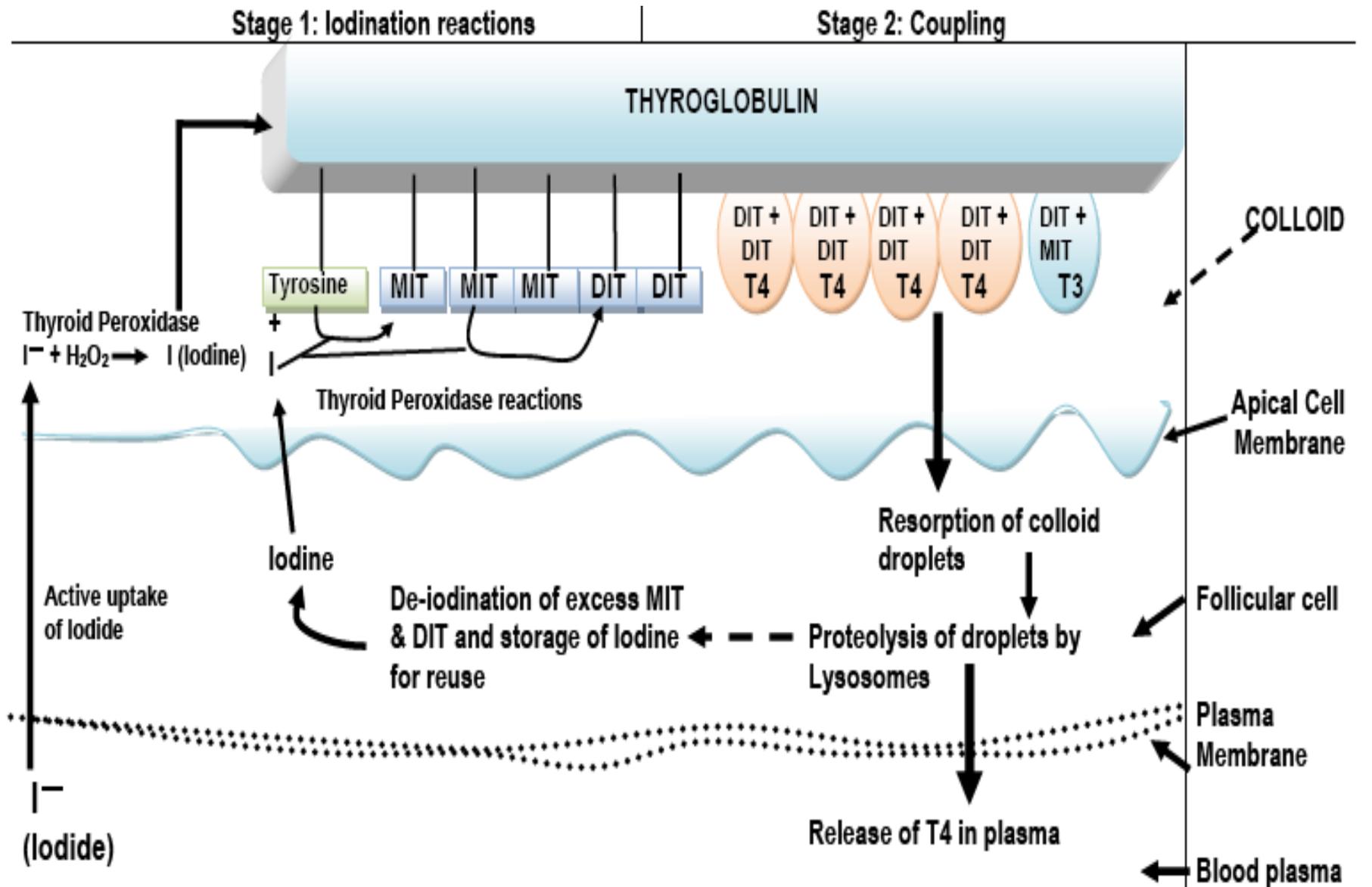
Stage One: Iodination Reactions (or Organification):

- Trapping of **Iodide** from plasma by Thyroid gland,
- Oxidation of Iodide (I^-) to Iodine (I) by **Thyroid Peroxidase** using Hydrogen Peroxide ($H_2 O_2$),
- Thyroid Peroxidase then uses Iodine to Iodinate Tyrosine residues attached to Thyroglobulin (TG), forming **3-Monoiodotyrosine (MIT)** residues,
- Thyroid Peroxidase iodinate MIT residues **Second time** to form **3,5-Diiodotyrosine (DIT)**;
- Both **MIT** and **DIT** still remain attached to TG;

Stage Two: Coupling Reactions:

- Thyroid Peroxidase cleaves off **MIT** or **DIT** and **Couples** it to **Acceptor DIT residues on TG**,
- Three combinations can occur:
 - **DIT + DIT** coupling gives **T4**,
 - **MIT + DIT** coupling gives **T3**,
 - **DIT + MIT** gives **r T3** (inactive hormone),
- **Major coupling reaction is formation of T4**,
- Finally, T4 and T3 are released into plasma,
- Thyroid gland secretes mostly T4 into plasma;
- **Fig. 1: Diagram of biosynthesis of Thyroid Hormones**

Fig. 1: Schematic diagram: Biosynthesis of Thyroid Hormones



How is T4 utilized in peripheral tissues? (Production of T3 in peripheral tissues)

- **T4**: Pro-hormone produced by Thyroid gland,
- **Biologically active Thyroid hormone is T3**,
- Liver and Kidneys have **De-iodinase** that De-iodinate **T4** to produce about two-thirds of **T3** in plasma,
- **De-iodinase** that catalyses conversion of **T4 to T3** requires trace element **Selenium**, because it contains a specific Amino Acid called “**Seleno-Cysteine**”,
- **5'-De-iodinase** that **does not** require **Selenium**, catalyses the conversion of **T4 to Reverse T3**,

- Deficiency of **Selenium** causes **decrease** in conversion of **T4 to T3**, resulting at the same time in increased conversion of **T4 to reverse T3 (rT3)** by **5'-Deiodinase** that **does not** contain **Seleno-Cysteine**,
- Other body cells containing Deiodinase can convert T4 to T3,
- Alternatively, T4 can be metabolised to Reverse T3 (rT3), which is biologically inactive,
- By modulating relative production of T3 and rT3, tissues can “**Fine Tune**” their local Thyroid Status,

What are some factors that affect conversion of T4 to T3?

- Several factors affect conversion of T4 to T3 in cells,
- Some factors decrease activity of De-Iodinase, thus increasing rT3/ T3 ratio, less T4 to T3 conversion,
- Other factors that affect T4 to T3 conversion include:
 - Pregnancy or oral contraceptive pills,
 - Fasting,
 - Stress,
 - High plasma Cortisol,
 - Catabolic diseases,
 - Hepatic and Renal diseases,
 - Thiouracil drugs (inhibits Thyroid Peroxidase activity)

How are the Thyroid hormones transported in plasma? (Thyroid Hormone Binding in Plasma):

- T4 & T3 are bound to specific plasma proteins:
 - Thyroxin-Binding Globulin (TBG),
 - Transthyretin (Thyroxin-binding pre-albumin or TBPA),
 - Plasma Albumin,
- TBG: important binding protein for Thyroid hormones,
- TBG is synthesized in the Liver;
- TBG binds about 70% of T4 and about 80% of T3,
- About 0.05% of T4 and 0.2% of T3 are Free in plasma (i.e., unbound to protein in plasma),
- Estrogens (pregnancy and birth control pills) increase the biosynthesis of TBG,

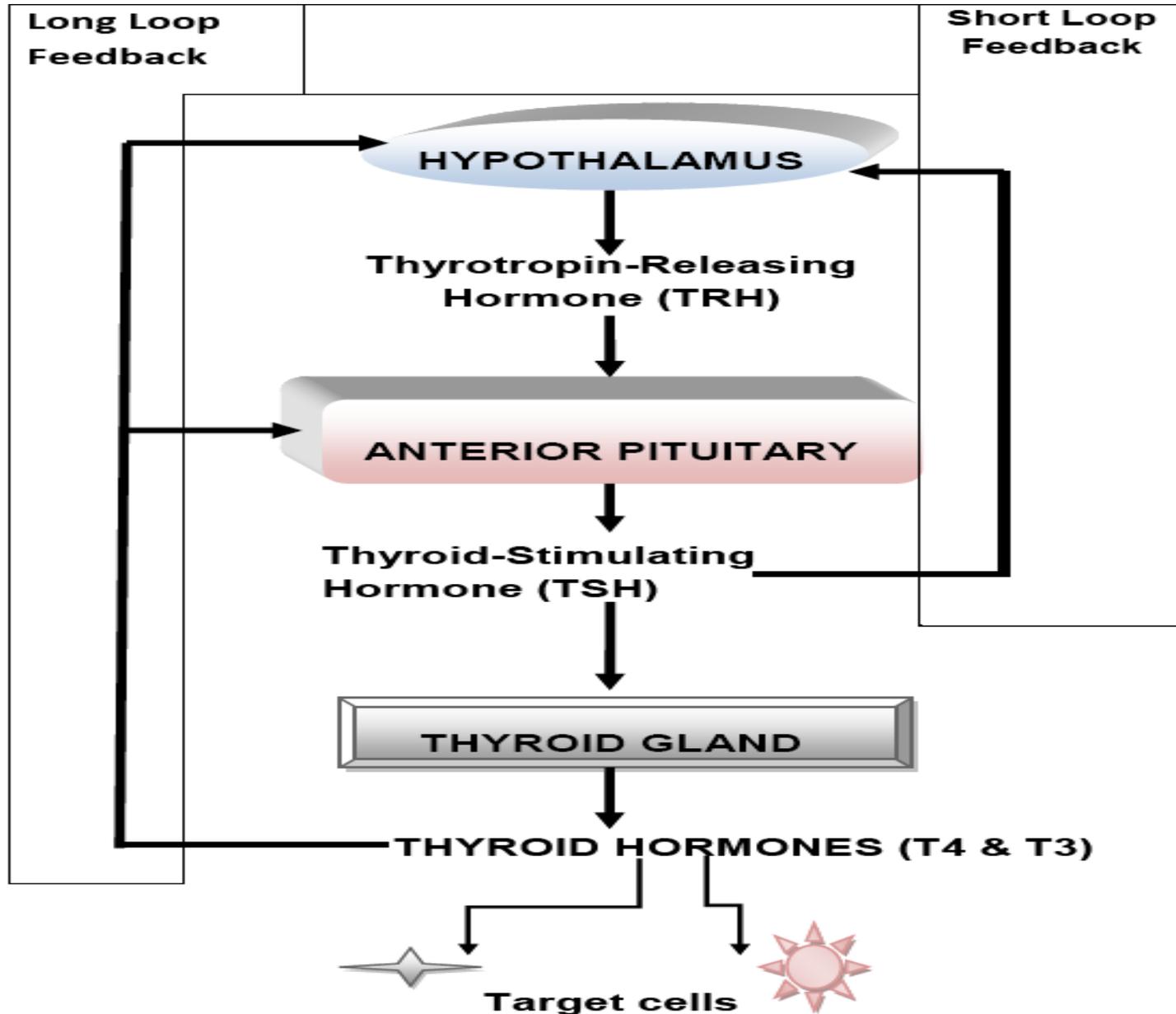
IMPORTANT TO NOTE

- Plasma contains both Bound and unbound (Free) Thyroid hormones,
- Amount of **unbound or “Free” T4 and T3 (FT4 and FT3)** are important for biological effects of Thyroid hormones, including feedback control to the Anterior Pituitary and Hypothalamus, (**Why?**)
 - Because only the Free Fractions can cross the cell membrane and affect intracellular metabolism;

How is the secretion of Thyroid hormones regulated?

- Feedback regulation of Thyroid hormones occurs via the **Hypothalamic-Pituitary-Thyroid axis (HPT axis)**, {Fig. 2}
- Hypothalamus secretes Thyrotropin-Releasing Hormone (TRH),
- TRH stimulates Anterior Pituitary to synthesize and release Thyroid-Stimulating Hormone (TSH),
- TSH stimulates Thyroid glands to produce T4 and T3,
- Excess FT4 and FT3 act via long loop feedback to block production of TSH and TRH,
- TSH blocks TRH production via short loop feedback,
- Knowledge of feedback regulation of HPT axis is essential for interpretation of results in investigation of thyroid status,

Fig. 2: Negative Feedback regulation of HPT-axis



IMPORTANT TO NOTE

- If Thyroid gland of a patient is producing too much Thyroid hormones, then the circulating TSH will be suppressed (**Why?**);
- If Thyroid gland of a patient is not secreting enough Thyroid hormone, the TSH level will be very high in an attempt to stimulate the Thyroid gland to secrete more Thyroid hormone;
- **Non-Thyroidal illness (NTI)**: a number of hormones and other agents inhibit the release of TSH;
- These include the following:
 - Dopamine, Somatostatin, Glucocorticoids, Interleukins

What are some cellular actions of Thyroid hormones?

- FT3 binds to high affinity receptors on membranes of target cells, and are actively transported into cells by ATP-dependent mechanism;
- In cells, FT3 enters Nucleus, binds to Hormone Response Elements (HRE) in DNA, which then cause activation of T3-responsive Genes;
- These genes exert a number of effects on cell metabolism, which include:
 - Stimulation of Basal Metabolic Rate,
 - Metabolism of Lipids, Carbohydrates and Proteins,

- Regulation of Gene Expression,
- Regulation of Tissue Differentiation,
- General Development, which are essential for the normal maturation and metabolism of all tissues,
- High plasma Thyroid hormone levels may cause increased Metabolic State by:
 - Increasing Mobilization of Endogenous Protein, Fat and Carbohydrate for production of substrates needed for Energy Production,

- Effects of Thyroid hormones on tissue maturation are seen in Congenital Hypothyroidism, a condition, which unless treated within a short time after birth, may results in permanent brain damage,
- Hypothyroid children have delayed skeletal maturation, short stature and delayed puberty,
- Example of the effect of Thyroid hormones on lipid metabolism is High Serum Cholesterol in some Hypothyroid Patients,
 - Due to reduction in cholesterol metabolism, caused by down regulation of LDL receptors on Liver cells with subsequent failure of Sterol excretion via GIT,

Summary of the actions of Thyroid Hormones on whole body metabolism

- Increase Basal Metabolic Rate (BMR),
- Increase Oxygen consumption,
- Increase Thermogenesis (heat production in the body),
- Activate $\text{Na}^+\text{-K}^+\text{-ATPase}$ in cells,
- Increase number of Mitochondria in cells,
- Increase mobilization of endogenous: Carbohydrate, Fat and Protein as substrates for energy metabolism,
- Increase Glycolysis, Glycogenolysis, Gluconeogenesis,
- Increase Lipolysis and Protein degradation,

- Decrease Muscle mass,
- Decrease Adipose Tissue,
- Increase Beta-Adrenergic receptors, which leads to increase Cardiac Output,
- Increase Systolic blood pressure only,
- Increase Ventilation Rate,
- Required for maturation of Ovary and Testis,
- Required for Actions of Growth Hormone (GH) to promote linear growth / bone formation,
- Required for development of CNS in Foetus,