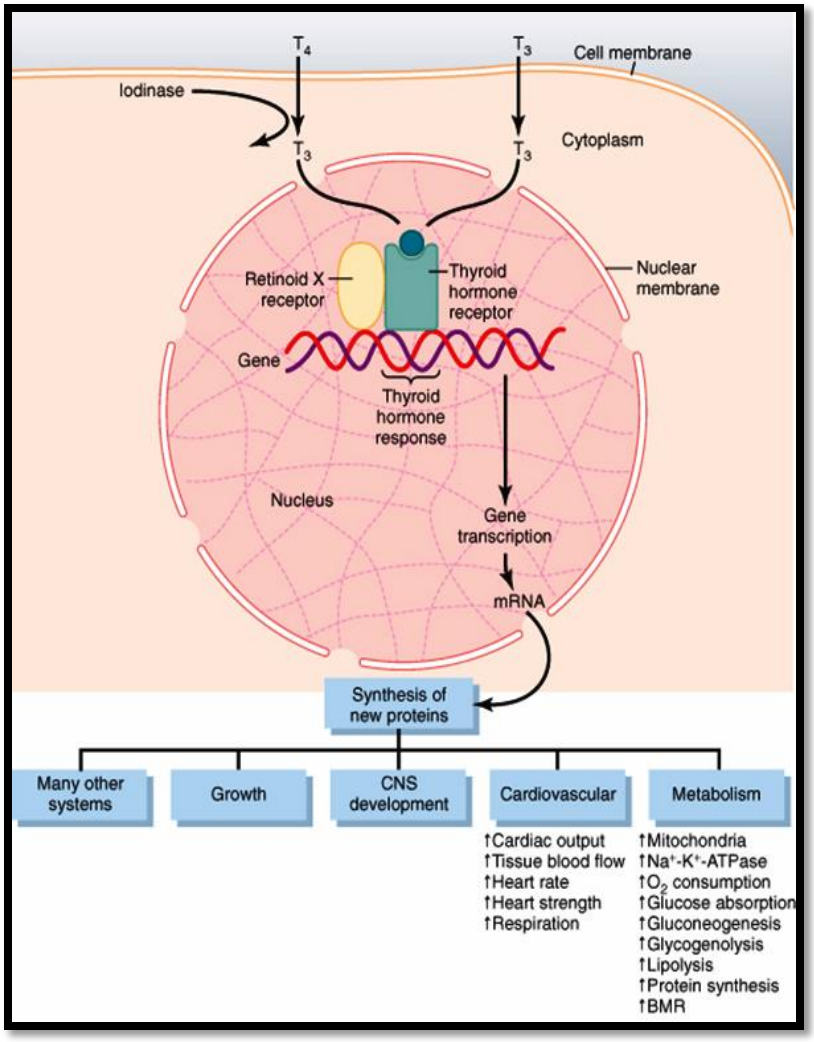
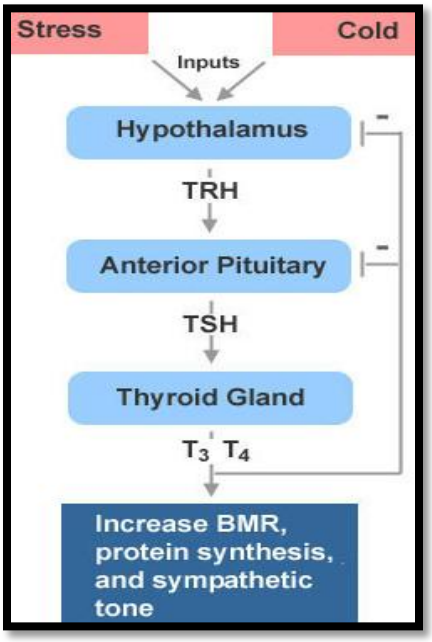
Unit IV – Problem 4 – Biochemistry: Thyroid Hormones

- Thyroid hormones are synthesized in the thyroid gland from the precursor (tyrosine). Iodine is very essential for production of thyroid hormones and its main source is ionized salt.
- The precursor of thyroid hormones (T3 and T4) is known as thyroglobulin and it is stored in colloid which is surrounded by follicular cells. Thyroglobulin is a large iodinated glycosylated protein.
  - 70% of iodine in thyroglobulin is found in inactive precursors: monoiodotyrosine (MIT) and diiodotyrosine (DIT).
  - 30% of iodine is in the form of T3 and T4.
- When iodine is sufficient, T4:T3 ratio is 7:1 (more T4 is produced from the thyroid gland).
- **Iodide metabolism:**
  - Iodide is transported from low concentration gradient (in the blood) to high concentration gradient (in thyroid gland) by active transport (sodium-potassium-ATPase transporter) → this process is known as iodine trapping.
    - ✓ Ratio of iodide in thyroid gland to that in the serum is 20:1
    - ✓ The iodide transporter can be inhibited by two classes of molecules:
      - ❖ Perchlorates.
      - ❖ Thiocyanate.
  - The thyroid gland oxidizes iodide to iodine by thyroperoxidase (with the presence of hydrogen peroxide H_2O_2).
  - Oxidized iodide will interact with tyrosine residues in thyroglobulin to form (MIT) and (DIT) → this process is known as thyroglobulin organification.
    - ✓ Coupling of two (DIT) forms T4.
    - ✓ Coupling of (MIT) with (DIT) forms T3.
  - Formed T4 and T3 remain as part of thyroglobulin until the later is degraded by lysosomal proteases (stimulated by TSH).
- **Transport of thyroid hormones:**
  - $t_{1/2}$ of T4 is 7 days while $t_{1/2}$ of T3 is 1-1.5 days (although it is more potent than T4!).
  - In plasma, thyroid hormones are bound to thyroxine binding globulin (TBG: produced in the liver and binds T3,T4 with 100 times affinity compared to TBPA) and thyroxine binding prealbumin (TBPA).
  - Only 0.03% of T4 and 0.3 of T3 are in unbound state and thus can express their biological activity by binding to their intracellular receptors. Notice that most of T4 will be converted to T3 in peripheral tissues.



- **Mechanism of action of thyroid hormones (see the image in previous page):**
  - They bind to their receptors in target cell nucleus.
  - Then, they induce general protein synthesis causing positive nitrogen balance via induction of repression gene transcription.
- **Regulation of thyroid hormone secretion:**



- **Thyroid diseases:**
  - **Goiter**: enlarged gland due to increased TSH due to deficiency, partial defects in Iodine metabolism and hormone synthesis. The inhabitants of areas in which the soil has a low iodine content often develop this condition. The small amount of NaI usually added to commercially available table salt easily prevents this iodine deficiency disease.
  - **Hypothyrodism**: Low levels of thyroid hormones due to thyroid failure, but could be due to disease of hypothalamus or pituitary gland (which control release of TSH). BMR (Basal Metabolic Rate) declines → affecting most of the body systems and can lead to slow heart rate, sluggish behavior, constipation, sensitivity to cold, dry skin/hair and affected speech.
  - **Hyperthyroidism**: Increased levels of thyroid hormones leading to raised BMR, palpitations, heat intolerance, excessive sweating, loss of weight, nervousness. There many causes of hyperthyroidism but the most common is Graves' disease (an autoimmune disorder).